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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

DECEMBER 1943

SERUM PROTEINS IN RELATION TO LIVER DISORDERS*

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INTRODUCTION

WITHIN recent years numerous studies have been made on the serum and plasma proteins.[1] It has been shown that they are concerned with the maintenance of tissue equilibrium or homeostasis. The component chiefly concerned here is the albumin fraction. The globulin portion of the serum has been shown to contain immune bodies. In this fraction also reside factors concerned with blood coagulation. Recent studies by Schoenheimer and others have shown that the serum proteins are substances which are in a dynamic state, constantly being formed and broken down, and that there is a ready exchange between the blood proteins and the body protein stores.[2,3]

Evidence is accumulating which suggests that certain of the plasma

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TABLE I

SERUM PROTEIN VALUES IN PATIENTS WITH ACUTE HEPATITIS

Serum Albumin grams per cent	*36 Cases at P.B.H.**	*35 Cases in Literature***
2.5 — 3.5	6	13
3.6 — 4.0	19	11
4.1 — 5.0	11	11
Serum Globulin grams per cent		
1.5 to 3.0	25	29
3.1 to 3.5	10	5
3.6 to 4.1	1	1

* Data obtained through courtesy of Drs. T. C. Chalmers and F. M. Hanger.
** Data obtained from 5 papers.[8-12]

proteins—namely fibrinogen, prothrombin and albumin originate within the liver. It is not surprising, therefore, to find changes in the blood protein constituents when the liver is disordered. The present paper is concerned with a number of these changes seen in liver disease.

ORIGIN OF SERUM PROTEINS

Albumin: Evidence for the liver as the site of origin of serum albumin is largely indirect. Experimental studies, especially those from Whipple's[3] laboratory, have shown that by poisoning the liver of dogs with carbon tetrachloride, the serum albumin level may be reduced. Furthermore, in dogs with Eck fistula or in those poisoned with chloroform or phosphorus, the ability to regenerate serum protein after plasmapheresis is impaired. These findings show that liver damage is associated with a reduced serum albumin level and a reduced capacity of the organism to form serum albumin. In addition, the liver plays an important role as a storage depot for protein.[4, 5] These observations seem to have their clinical counterpart in certain human diseases of the liver, to be discussed later.

Globulin: The evidence for the site of origin of the globulin fraction is less adequate. Sabin[6] has presented evidence suggesting that globulin may be formed in the reticulo-endothelial cells. She injected rab-

bits with a protein antigen conjugated with dye to make it visible, and she found that it was phagocytosed by reticulo-endothelial cells. After four to seven days, when antibody began to appear, the cells which had taken up the dye appeared to be shedding their surface films into the surrounding fluid. Sabin concluded from these studies that antibody was therefore formed from these cells. Since antibody resides in the globulin fraction of the blood proteins, she suggested that the reticulo-endothelial cells might be the site of origin for normal serum globulins. It is noteworthy that states of hyperglobulinemia are frequently associated with diseases in which there is a marked involvement of the reticulo-endothelial tissue, such as leukemia and multiple myeloma.

Fibrinogen and Prothrombin: There is much experimental evidence indicating that both these protein constituents are formed in the liver. Liver damage induced by hepatotoxin and by hepatectomy is associated with decreased plasma prothrombin and fibrinogen.[7]

Changes in Serum Proteins in Liver Disease

Acute Liver Disease: In acute hepatitis ("catarrhal" jaundice; arsphenamine poisoning; cinchophen poisoning) there generally is only moderate alteration in the serum proteins, as determined by salt precipitation methods. Table I shows the values for serum albumin and serum globulin in thirty-six patients with acute hepatitis on admission to the Presbyterian Hospital, and in thirty-five cases collected from the medical literature.[8-12] In most instances these determinations were made within two weeks of the onset of jaundice. If 4 grams per cent of serum albumin be considered the lower limit of normal, roughly two-thirds of the series showed decreased albumin, but the degree of reduction was slight. Likewise if a value of 3.0 grams per cent of serum globulin be taken as the upper limit of normal, roughly one-fourth the series showed slight increase of this fraction. When the disease process is more protracted or severe, as in acute or subacute yellow atrophy, these changes in serum proteins may become very pronounced. Finally, in the stage of chronic hepatitis or cirrhosis of the liver, the serum albumin characteristically is reduced. These findings may indicate that in acute hepatitis the body and liver stores for serum albumin are sufficient to tide over the emergency of a short lived disease. Since the tissue depots are drained first, a decrease in the serum albumin might not appear until the stores were depleted.

Although values for serum globulin may be only slightly altered in acute hepatitis, as seen in Table I, there is generally a qualitative change in the globulin component, which is considered to be more or less distinctive for liver damage. This qualitative change apparently resides in the euglobulin fraction,[13, 14, 15] and it is reflected by such tests as the cephalin flocculation reaction, Takata-Ara reaction and colloidal gold test.[16]

Significant changes of plasma fibrinogen seldom are seen in either acute or chronic hepatitis unless the disease process is advanced, as in acute yellow atrophy. This implies that the reserves for this clotting factor are far in excess of normal demands.

Studies with experimental animals have shown that the prothrombin level is decreased more rapidly than fibrinogen following hepatectomy or chloroform poisoning.[7] Clinical observations bear this out, since changes in prothrombin occur rapidly after the onset of acute hepatitis. This suggests either that the body stores are less ample, or that prothrombin is a more labile substance which is readily exhausted or destroyed by liver damage. Moreover the administration of vitamin K fails to restore a normal value for prothrombin in the presence of severe liver damage. This failure of the organism to respond to vitamin K has been used as a test for impaired liver function.[17] Since much has been written on this subject, we should prefer not to dwell on it further at this time, but rather to discuss changes of the serum proteins in chronic liver disease, with which we have had more experience.

Chronic Liver Disease: The serum proteins are consistently altered in cirrhosis of the liver. The original observation of Filinski,[18] showing a decrease of serum albumin and increase of serum globulin in the presence of cirrhosis of the liver, has been confirmed from many sources.[19] During the course of a study of this disease, begun in 1936, repeated observations were made on the serum proteins in many patients. Some of the results of this study have been recorded elsewhere.[20, 21, 22, 23] Figure 1 shows the frequency distribution of the serum albumin and globulin levels of sixty-one patients with cirrhosis of the liver on entry to the hospital. These patients exhibited various stages of the disease process. Some had ascites with jaundice, whereas others had only ascites or jaundice. In still others the presenting problem was hematemesis. The data in this chart confirm the reported tendency toward reduction of serum albumin and elevation of serum globulin in this disease.

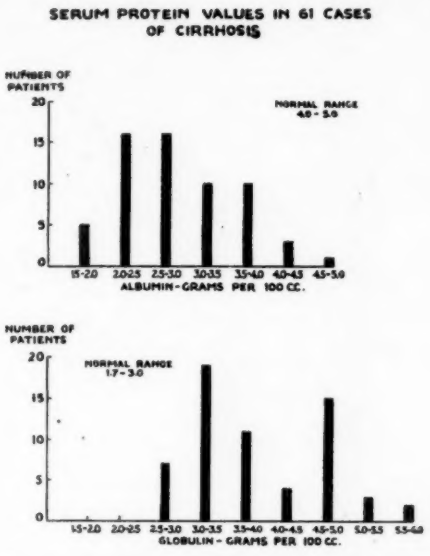
SERUM PROTEIN VALUES IN 61 CASES OF CIRRHOSIS
NUMBER OF PATIENTS
NORMAL RANGE 4.0 - 5.0
ALBUMIN - GRAMS PER 100 CC.
NUMBER OF PATIENTS
NORMAL RANGE 1.7 - 3.0
GLOBULIN - GRAMS PER 100 CC.

Fig. 1—*Frequency distribution of serum proteins in 61 cases of cirrhosis of the liver.* The serum albumin tends to be reduced and the serum globulin to be increased.

Relation of Serum Proteins to the Clinical Course of Laennec's Cirrhosis: A number of authors[8, 9, 10, 11, 24] have suggested that there may be a correlation between the severity of liver disease and alterations in the serum albumin and globulin. We have analyzed our data with respect to this problem. Of twenty patients who died after an average hospital stay of three months, the mean level of the serum albumin was 2.4 grams per cent on entry to the hospital. Of twenty-eight patients who improved, as measured by disappearance of ascites and gain in weight and strength, the mean value for the serum albumin was 3.0 grams per cent, on admission. The difference between these two levels is statistically significant. Figure 2 shows the frequency distribution of the albumin values of these two groups of patients.

All of the twenty patients who died had ascites, and but two showed a temporary improvement. Their admission serum albumin levels were 2.9 and 3.3 grams per cent, respectively. Of these twenty patients who died, 70 per cent had albumin levels below 2.5 grams per cent on admission. Of the twenty-two patients who had ascites on admission, but

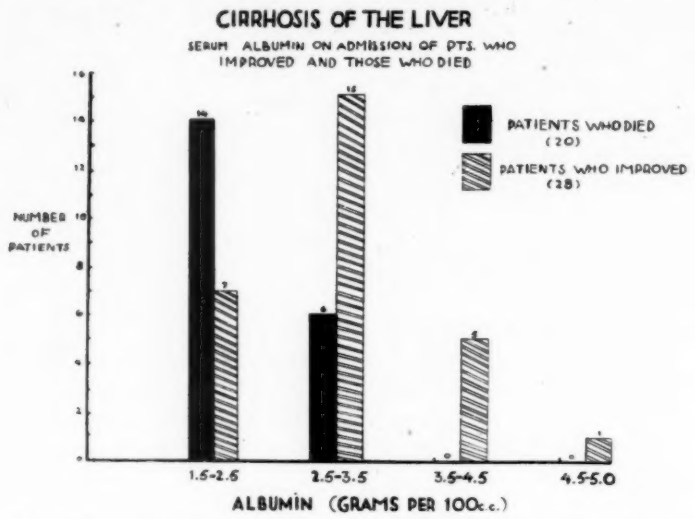

Fig. 2—*Frequency distribution of serum albumin in relation to prognosis as to duration of life.* This chart shows the values on admission to the hospital. The initial serum albumin values were lower for patients who subsequently died than for those who improved.

who improved subsequently, 70 per cent had albumin levels greater than 2.5 grams per cent. Thus it appears that the prognosis as to duration of life becomes increasingly grave as the serum albumin level decreases.

Examination of the values for the serum globulin and serum total proteins fails to reveal any significant differences between the patients who improved and those who died.

Wiener and Wiener[8] cited three cases in which changes of the serum proteins correlated fairly well with the clinical course of the patients. Foley, Keeton, Kendrick and Darling[11] reported data on one patient with cirrhosis of the liver and ascites, whose ascites disappeared and whose clinical improvement was associated with a return of serum protein values to normal during a period of seven months. Conn, Newburgh, Johnson and Sheldon[25] recorded data on the serum proteins of one patient with chronic liver disease, in whom improvement was associated with a rise in serum albumin to normal. The patient had no ascites. Except for these few instances there has been little recorded evidence indicating that changes in serum proteins may reflect changes in the disease process. We have examined the serum protein levels of

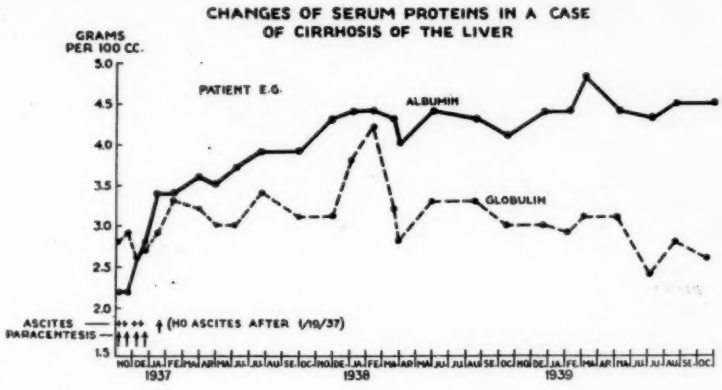

Fig. 3—Serum proteins in a patient who showed clinical improvement.

our patients in order to determine whether there is any correlation between the blood protein fluctuations and the clinical course.

Figure 3 shows the value of serum albumin and globulin in a patient who improved and remained in good general health for more than three years. On admission the serum albumin was very low, and the globulin was elevated. Repeated paracenteses had been performed for several months prior to hospitalization and during the first portion of the hospital stay. With clinical improvement there was a sustained rise of serum albumin to normal values. The globulin tended to fall. From 1939 to 1942 she has been well except for one period of decompensation with ascites, which was associated with a decrease in serum albumin. She recovered from this, and she has been well for the past one and one-half years. This pattern of response has been seen repeatedly in patients who have improved and remained in good health.

In contrast to the above findings, Figure 4 illustrates changes of serum proteins in a patient whose course was that of clinical failure. This patient, who was very ill at entry, required frequent paracenteses. After nine months in the hospital the patient died. The progressive decline of serum albumin is typical of this group. However, the decline of serum globulin observed in this patient is not usually encountered.

There is a third group of patients which seems to conform to a third pattern. Figure 5 charts the serum proteins of such a patient. On admission this man had massive ascites, edema and jaundice. Repeated

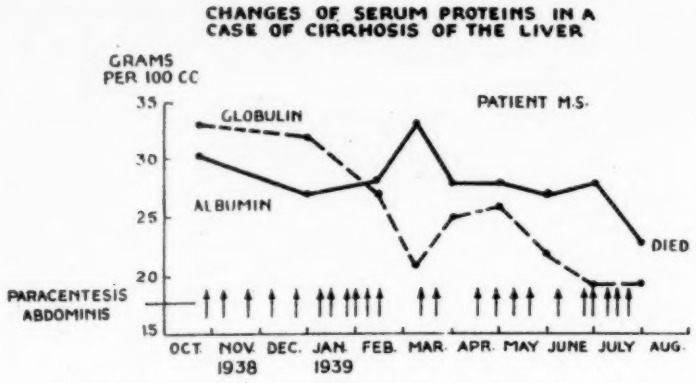

Fig. 4—Serum proteins in a patient with clinical failure.

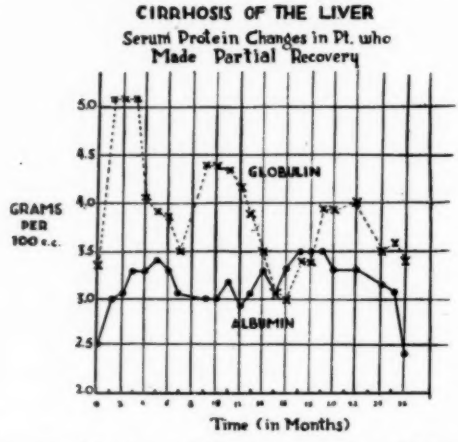

Fig. 5—Serum proteins in a patient who showed partial improvement.

paracenteses had been performed in the past. During the first six weeks of hospitalization there was marked clinical improvement with loss of ascites, and subsequent weight gain of 20 pounds. For the next two years he remained in fairly good health but the serum albumin, after an initial rise, did not return to normal. After about two years of hospitalization he was permitted to leave. He returned after three weeks with massive edema and ascites, and he died within three days. There was a sharp decrease in serum albumin before death. The diagnosis of cirrhosis of the liver was confirmed at necropsy. This pattern of blood

proteins has been seen in other patients who lost ascites and improved clinically for long periods of time, but whose course was ultimately unfavorable.

From these data it appears that the changes in level of the serum albumin have a good correlation with the clinical course. In those patients who improve and remain in good health for indefinite periods of time, the serum albumin rises to normal values and remains within that range. In those patients who show only temporary improvement, the serum albumin increases but does not reach normal levels. Here the prognosis is guarded despite temporary states of apparent well-being. In those patients whose course is unfavorable, the serum albumin either remains low or declines.

Relation of Serum Protein Level to Formation of Ascites

Following Starling's[26] work on the role of the serum proteins in the maintenance of the colloid osmotic pressure of the blood, numerous investigators have stressed the important relationship between alterations in the blood protein level, particularly the albumin level, and the transudation of edema fluid. In the edema of nephrosis,[27, 28] nephrotic stage of glomerulonephritis[29] and in protein starvation,[30] this correlation has been shown. With regard to ascitic fluid in cirrhosis of the liver, Loeb, Atchley and Palmer[31] have shown that it has the properties of a transudate. Many workers have presented data to show a correlation between the reduced level of the serum albumin and the accumulation of ascites.[9, 32, 33]

Our data are in accord with these reports. Figure 6 shows the frequency distribution of serum albumin levels in forty-three patients with ascites and in twenty-eight patients without ascites. The values for the forty-three patients with ascites were obtained on admission to the hospital. Values for serum albumin in patients without ascites were derived from two sources. In thirteen cases the data are admission values, whereas in fifteen cases the data are values in patients who lost ascites during their hospital stay. Values for the latter group were taken two months after diuresis was considered complete. The mean serum albumin level for the patients with ascites was 2.3 ± 0.1 grams per cent, whereas that for the patients without ascites was 3.7 ± 0.8 grams per cent. The difference between these values is statistically significant. The values for serum globulin and serum total protein are not signifi-

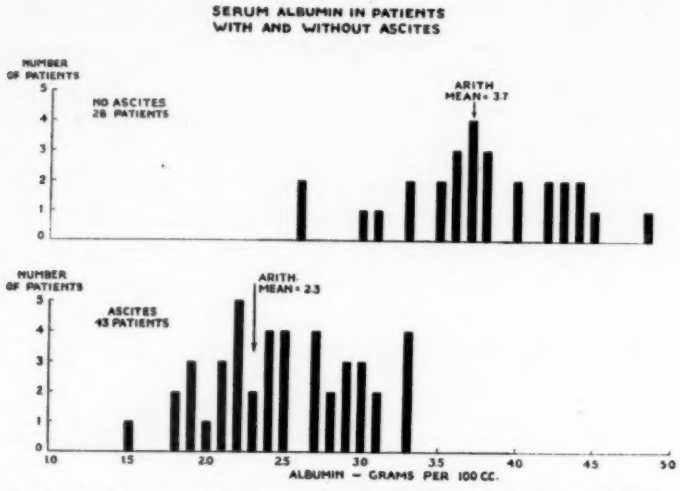

Fig. 6—Frequency distribution of serum albumin in patients with and without ascites. The serum albumin is significantly lower in the group with ascites. (B)

cantly different. Thus the accumulation of ascites may be correlated with the level of the serum albumin. There is another important factor in the formation of ascites, namely, portal hypertension. Thompson, Caughey, Whipple and Rousselot[34] have demonstrated splenic vein hypertension in Banti's syndrome. Bellis[35] has demonstrated portal hypertension in one patient with cirrhosis of the liver and ascites, and McIndoe[36] has shown increased resistance in the cirrhotic liver to perfusion via the portal vein. It seems likely that reduced serum albumin is an essential factor in the transudation of the fluid, whereas portal hypertension determines the site at which the transfer of fluid takes place. The serum globulin does not seem to play a critical role. These data have been helpful in evaluating the course of ascites in particular patients. We have observed that when ascites occurs in the presence of normal serum albumin, one should suspect an extrahepatic cause, such as portal vein thrombosis or carcinoma involving the porta hepatis, as a contributory factor to the accumulation of ascites.

Relation of the Serum Protein Level to Diuresis

In 19 instances of diuresis in 17 patients, the mean serum albumin level at which this phenomenon occurred was 3.1 grams per cent and

the mean serum globulin level was 4.1 grams per cent. It is difficult to establish the time at which the onset of diuresis takes place because this phenomenon may persist for weeks. However, the serum albumin level of 3.1 is near the transition point between the two groups of patients noted in Figure 6. It is noteworthy that the level of 3.1 grams is higher than the commonly accepted critical level for edema of 2.5 grams in hypoproteinemia from other causes. This may be due to the added factor of portal hypertension. It is seen that the serum albumin rises in patients who improve and lose their ascites. This may not necessarily represent a "cause and effect" relationship, since both phenomena might reflect improved liver function.

Nitrogen Balance in Cirrhosis of the Liver

Data have been presented which show that the liver plays an important part in the formation of serum albumin. From the afore-mentioned clinical studies, it appears that the level of the serum albumin may be correlated with the clinical course of cirrhosis of the liver, as well as the appearance and disappearance of ascites. We are next concerned with the cause of this protein abnormality in liver disease.

Some authors[37] have ascribed the decreased serum albumin of cirrhosis of the liver to insufficient protein intake, whereas others[9, 11] have suggested impaired protein synthesis as the mechanism. It is obvious that hypoalbuminemia could be caused by protein starvation, by excessive utilization, or by impaired synthesis.

Patients with starvation hypoalbuminemia differ from those with low serum albumin in liver cirrhosis in that elevated serum globulin seen so commonly in cirrhosis, does not occur. The reduction in serum protein is at the expense of the albumin alone in starvation. In cirrhosis of the liver the total protein is usually normal. A second point of difference is that the low serum albumin of starvation generally responds within ten to twenty days with a rise in serum albumin, if one or two grams of protein be fed per kilogram of body weight per day.[38] Although the antecedent diets of patients with cirrhosis of the liver are deficient in protein sources, such as meat and dairy products, these individuals do not show such prompt improvement in serum albumin after high protein feeding.[21] Furthermore, the experimental studies reviewed by Madden and Whipple[3] show that the low serum albumin levels in dogs, maintained on a low protein diet and plasmapheresis, may be

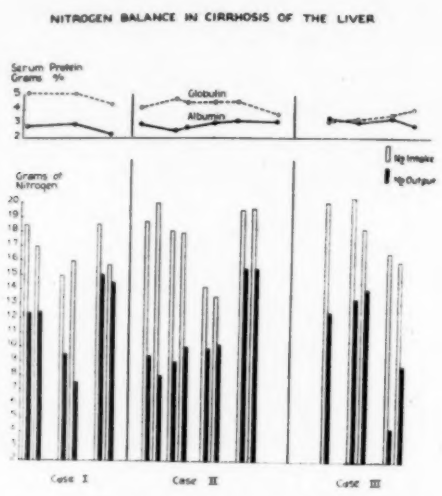

Fig. 7—Nitrogen balance studies in 3 patients with cirrhosis of the liver. Although all patients were in positive nitrogen balance there were no changes in serum proteins.

rapidly restored to normal after adequate protein feeding. When dogs are kept on low protein intake for twenty-one days rapid restoration of serum albumin to normal occurs. However when the period of low protein feeding is maintained for long intervals, eighty-five days or more, regeneration of serum protein levels to normal is impaired.[39] After prolonged periods of low protein feeding, histological[39] and functional changes[40] are said to occur in the liver. These changes may be part of a pattern of impaired liver function with associated faulty albumin synthesis.

In order to determine the nature of the hypoalbuminemia of cirrhosis of the liver, nitrogen balance studies were performed in 5 patients with low serum albumin and ascites. Grabfield and Prestcott[41] have reported positive balance in one patient with cirrhosis who had normal serum proteins. Although balance studies were not performed, Myers and Keefer[9] showed that high protein feeding over a limited period of time did not produce changes of serum albumin in 4 patients with decompensated Laennec's cirrhosis. In the present balance study, patients were fed a standard diet (containing C 280, F 100, P 100) for 4 to 6 weeks before the study was begun. In three subjects the nitrogen bal-

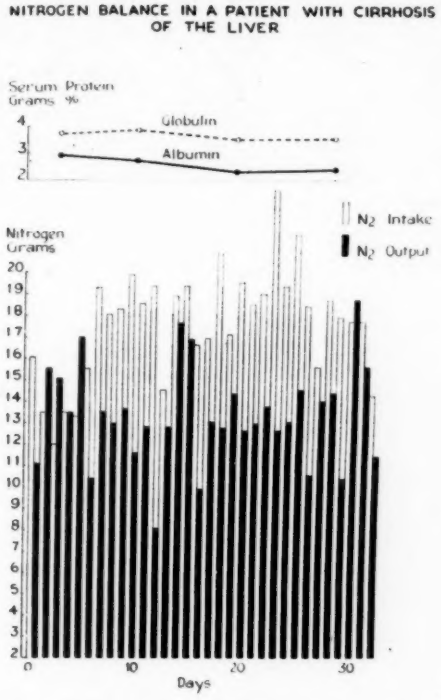

Fig. 8—Nitrogen balance in one patient with cirrhosis of the liver studied for 32 days. The findings are similar to those in Figure 7.

ance was determined for forty-eight hour periods at two week intervals. Figure 7 shows the results in this group. In two subjects the daily balance was determined for twenty-five and thirty-two days respectively. Figure 8 represents the findings in the latter study. In all instances the patients were in positive balance. They were retaining nitrogen. In addition, normal values for fecal nitrogen showed that gastrointestinal absorption was normal. In no instance was there a sustained and striking rise in the serum albumin. The non-protein nitrogen and serum globulin levels did not reflect this retention of nitrogen. For example, one patient (Figure 8) retained 849 grams of protein as nitrogen, without a significant increase in the blood protein or non-protein nitrogen constituents.

This type of balance pattern differs clearly from that found in

nutritional hypoproteinemia.[38, 42] Whipple[43] has shown that there normally exists a ready exchange between the body protein stores and the blood proteins, and that the latter are reduced only after the body protein stores have been depleted. When protein is made available there is a rapid rise in blood protein level. It appears from the data presented, that in the patients with cirrhosis of the liver and hypoalbuminemia, the restoration of the serum albumin to normal is impaired. It is likely that the retained nitrogen is being converted to body protein and not to blood protein (albumin), a change from the normal which suggests faulty synthesis of serum albumin.

Summary and Conclusions

Evidence has been reviewed which indicates the liver as the probable site of formation for blood albumin, fibrinogen and prothrombin. Data have been presented to show the effects of liver disease, acute and chronic, on the protein constituents of the blood.

In acute liver disease the fibrinogen and prothrombin levels may be reduced. The albumin may show slight reduction and the globulin moderate elevation. In more severe forms of acute liver disease these changes may be pronounced.

In chronic liver disease, notably cirrhosis of the liver, the serum albumin generally is reduced, whereas the serum gobulin is normal or increased. The degree of reduction in the albumin level seems to be correlated with the prognosis as to duration of life, clinical course of the disease, and with the appearance and disappearance of ascites.

Nitrogen balance studies in cirrhosis of the liver show that patients with this disease can absorb and retain protein, but that there is an apparent defect in synthesis of serum albumin.

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DIAGNOSTIC SIGNIFICANCE OF SERUM ALKALINE AND ACID PHOSPHATASE VALUES IN RELATION TO BONE DISEASE*

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PHOSPHATASE, like enzymes in general, is known by its activity. This activity is manifested in: (1) the liberation of inorganic phosphate through hydrolysis of organic phosphorus compounds; and (2) under changed conditions, the utilization of inorganic phosphate in the synthesis of organic phosphorus compounds. As our title implies, there is more than one phosphatase, and indeed there are many. The pH at which the optimum activity of a phosphatase takes place furnishes a basis for the broad classification of phosphatases as so-called alkaline and so-called acid phosphatase 5. The former acts optimally at a distinctly alkaline pH (for instance, pH 9) and the latter at a distinctly acid pH (for instance, pH 5).

The alkaline phosphatase is by far the more widely distributed in the tissues of man. It is found in relatively high concentrations in the intestinal mucosa, kidneys, liver, ossifying cartilage, bone, and leukocytes. It is also normally present, but in relatively smaller amounts, in the blood serum. In regard to the functions of alkaline phosphatase in vivo, there is some evidence that it plays a role in the absorption of glucose through the intestinal wall, the reabsorption of glucose in the renal tubules, and the formation of osseous tissue.

The acid phosphatase is found in particularly high concentrations in the prostate after puberty. It occurs especially in the acinar epithelium of that gland; is apparently elaborated by this epithelium; and is excreted as a constituent of the prostatic fluid. The spleen and brain, too, contain a good deal of this phosphatase, though by no means as much

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as the prostate. It is present in other tissues, also, including the red blood cells, at least in small amounts. The serum shows extremely little acid phosphatase activity—in fact, much less even than alkaline phosphatase activity. As to the function of acid phosphatase, much further elucidation is needed. In vivo as well as in vitro it seems to play a role in glycolysis through its action on hexose phosphates. In the prostatic ejaculate of man it may, by this means, help to provide the energy required by spermatozoa for survival and motility.[1]

Before proceeding, it may be well to point out that the alkaline phosphatase and acid phosphatase categories apparently comprise a number of phosphatases which are not identical. However, the secondary differences between, for instance, the alkaline phosphatase of the intestine and that of the kidney, or between the acid phosphatase of the prostate and that of the spleen, need not occupy us here.

What we are concerned with is exclusively the alkaline phosphatase and acid phosphatase activity of the serum, and the significance of aberrations of their values in relation to disease, especially of the skeleton. Under conditions of disease, the alkaline phosphatase activity level of the serum may fall below or rise above the normal level. Elevations of this level are more significant and more common than drops, and are associated particularly with skeletal disorders and disorders of the liver and biliary passages. The acid phosphatase activity is significant diagnostically in that it nearly always rises above the normal level in cases of carcinoma of the prostate which has metastasized. Indeed, a high acid phosphatase activity value has come to be regarded as an important indication of the presence of this disease.

Estimation of Serum Alkaline and Acid Phosphatase Activity

The methods for the determination of alkaline phosphatase activity of serum (or plasma) were developed first. The method of Kay,[2] published in 1930 and used in some of the earliest clinical investigations of serum phosphatase activity, was soon found impractical, even by Kay himself. It was replaced in 1932 by that of Jenner and Kay,[3] but the latter method seems likewise to have been largely abandoned. On the other hand, the method of Bodansky,[4] first briefly reported in 1931 and fully described in 1933, came to be widely employed and apparently still is. The only other method which seems to be extensively used for the determination of the alkaline phosphatase of the serum is that of

King and Armstrong,[5] published in 1934. Both the Bodansky method and the King and Armstrong method have since been adapted to the determination of serum acid phosphatase activity also.

The principle underlying the Bodansky method of determining alkaline phosphatase activity is the estimation of the amount of *phosphorus* liberated as phosphate ions by a given amount of serum, incubated with a substrate containing sodium beta-glycerophosphate buffered to a constant alkaline pH of 8.6 by sodium diethylbarbiturate. The phosphatase activity value of any particular serum specimen is expressed in units. Specifically, this value, as determined by this method, represents the calculated number of mg. of phosphorus which 100 cc. of the serum can liberate in one hour as phosphate ions from the buffered substrate under the conditions of the test.

The principle underlying the King and Armstrong method of determining alkaline phosphatase activity is the estimation of the amount of *phenol* liberated by a given amount of serum incubated with a substrate containing disodium phenyl phosphate buffered to an alkaline pH of 9.0, again by sodium diethylbarbiturate. The units of phosphatase activity of any particular serum represent the calculated number of mg. of phenol which would be liberated by 100 cc. of the serum in one-half hour under the conditions of this test method.

As noted, both the Bodansky and the King-Armstrong methods for the determination of serum alkaline phosphatase activity can be adapted to the determination of serum acid phosphatase activity. The adjustment depends essentially upon the use of a substrate-buffer combination which (at least theoretically) will completely inhibit the activity of the alkaline phosphatase of the serum and at the same time permit optimal activity of the small amount of acid phosphatase which is also present.

Gutman and Gutman[6] adapted the method of King and Armstrong to the measurement of acid phosphatase activity by using a mixture of citric acid and sodium hydroxide as the buffer for the sodium phenyl phosphate substrate (to bring the pH to 4.9) and incubating for one hour. In our laboratory, the Bodansky method for determining serum alkaline phosphatase activity is adapted to the determination of serum acid phosphatase activity by adding acetic acid to the sodium beta-glycerophosphate-diethylbarbiturate substrate (so as to bring its pH to 5.0) and incubating for three hours.[7] The acid phosphatase activity value of the serum equals the calculated number of mg. of phenol or

phosphorus, respectively, which 100 cc. of the serum can liberate in one hour from the buffered substrate under the standard conditions of the tests.

Range of Values for Serum Alkaline Phosphatase

For alkaline phosphatase as determined by the Bodansky method, most values for adults range between 2.0 and 3.5 units per 100 cc. of serum and average about 2.8 units. In fact, they lie so strictly within this range that any value even very slightly above 4 units may be suspected of being abnormal. For children, the normal values lie between 5 and 14 units and average about 7.5 units. Values of 10 to 14 units are more likely to be found in children between the ages of ten and fifteen than in those up to ten years of age. In children, values near the upper limit of the normal range should arouse attention, and values of 18 units or more are to be considered clearly abnormal. For infants a few months of age, the normal values lie between 10 and 20 units and values between 20 and 25 are not yet necessarily abnormal, though they deserve special attention.

For alkaline phosphatase, as determined by the method of King and Armstrong, most values for adults lie between 5 and 10 units per 100 cc. of serum and average about 8 units. Values below 3 and above 13 begin to fall within the range of the abnormal. King and Armstrong themselves give but few data on the values for children, but reports by others using their method indicate values of 15 to 25 for children, with an average of about 20.

Serum Alkaline Phosphatase Values In Relation To Disease*

As noted, under conditions of disease in the body, the serum alkaline phosphatase value may either fall below or rise above the normal level. Values below 2.0 Bodansky units are observed occasionally in "normal" adults. More regularly they are found in adults suffering from surgical hypoparathyroidism. Cachectic adults, also, very often show abnormally low values, even if the cachexia has developed on the basis of malignancy, provided the latter is not metastatic to the liver or skeleton.

* These values will be stated throughout in terms of Bodansky units only. Within the normal range the Bodansky values are roughly about ½ as great as the King-Armstrong values. However, in the abnormal range, this proportionality no longer holds, the Bodansky values rising very much more steeply. Thus, one cannot, in the high upper range, convert a Bodansky value into a King-Armstrong value or vice versa by multiplying or dividing, respectively, by 3. Control study of the question of high abnormal values by the use of mixed sera leaves no doubt in our mind of the accuracy of the high values as determined by our method.

On the other hand, a pronounced leukocytosis tends to increase the value slightly, often not even beyond the upper limit of the normal (4.0 units).

We pass on now to consideration of the numerous disorders of the skeleton in which elevation of serum alkaline phosphatase values may have considerable diagnostic significance. Our experience in this connection runs back over more than 10 years and followed closely in the wake of the studies by Kay[8] and Roberts.[9] Between 1931 and 1939, we published a number of articles,[10] both clinical and experimental, containing abundant data on elevations of the serum alkaline phosphatase value in relation to skeletal (and also hepatic) disorders. These findings have been corroborated by others[11] and continue to be confirmed by our current experience, based on a large volume of additional clinical and experimental material. Here, therefore, we are limiting ourselves, in the main, to summaries of, and conclusions from, this experience.

Before proceeding, however, we wish to point out that an abnormally high serum alkaline phosphatase value, though it does have diagnostic significance, frequently has to be considered in conjunction with other blood chemistry data in arriving at a definite diagnosis. It is true that even by itself a spectacularly high serum alkaline phosphatase value in an adult (100 to 150 units) almost surely indicates the presence of Paget's disease, and in a young child (75 to 100 units) rickets. On the other hand, an abnormally but not spectacularly high serum alkaline phosphatase value must often be considered in the light of the serum calcium, inorganic phosphate, NPN, and total protein values when one is attempting definitive diagnosis of a skeletal abnormality.[12]

In evaluating elevations of the serum alkaline phosphatase in the differential diagnosis of bone disease it must always be borne in mind that high alkaline phosphatase values are found also in connection with various disorders of the liver, including those of the biliary passages. Therefore, before drawing conclusions on the relation of a high phosphatase value to skeletal involvement in a given case, it is necessary to consider the possibility of involvement of the liver. We do not wish, however, to enter into the particularly complex question of the significance of elevated serum alkaline phosphatase values in relation to the differential diagnosis of liver disease with or without jaundice. We wish merely to point out that it is important in connection with hepatic dis-

orders, just as in skeletal disorders, to interpret the elevated alkaline phosphatase value in the light of other findings. Specifically, in connection with hepatic disease, the elevated alkaline phosphatase value must be considered in the light of the serum cholesterol value, cholesterol ester (or free cholesterol) per cent, bilirubin value, protein fraction values, and cephalin flocculation test result.

Paget's Disease: To date, we have accumulated findings on about 70 cases of this disease. In fully half of these the disease was of limited extent (that is, involved at most only a few bones). The cases presenting limited involvement yielded alkaline phosphatase values ranging between 5 and about 25 units and distributing themselves rather evenly along this range. On the other hand, in the cases presenting widespread skeletal involvement, the values, with few exceptions, ranged between 50 and 125 units. One exception was a case in which it was only 15 units, and this was the only case in which it was below 50 when the skeletal involvement was extensive. The explanation for the low value in this case may be that the disease had gone on to healing, as was revealed by histologic examination of many bones removed at autopsy. The highest value observed among our patients with widespread Paget's disease was 258 units. The dramatically high value in this case may be related to the fact that many of the involved bones were the site of osteogenic sarcoma.

Altogether, one can take the alkaline phosphatase activity value as a rough index of the severity of the disease process, and cases of Paget's disease showing values of about 75 to 150 units are certainly very active clinically. It is also of interest that ordinarily, so far as any particular case is concerned, the phosphatase value does not tend to vary much, at least over an interval of a year or so. Indeed, we have observed only one case which violated this rule. In that case, the phosphatase value doubled in the course of 16 months, rising from 70 to 142 units. Subsequently, this patient died of sarcoma complicating the Paget's disease.

Finally, it should be noted that in Paget's disease the serum calcium and phosphorus values are ordinarily normal. However, it has been found that an occasional case of Paget's disease is complicated by, or at least concomitant with, hyperparathyroidism. In these cases, a definite hypercalcemia is of course present, but the fact that removal of the offending parathyroid tissue has no influence upon the course of the Paget's disease indicates the independence of the two disorders.

Rickets of Infancy and Early Childhood: This is another disease in which the serum alkaline phosphatase value may be found very high. To date we have accumulated pertinent findings on about 100 cases. Some of the affected infants and young children had had no antirachitic therapy, while some had had inadequate therapy; some were admitted with full-blown rickets and even tetany, and others with substantially healed rickets and residual deformities. In short, these cases represent the variety of rachitic material which usually accumulates in hospital practice. Accordingly, our cases presented a wide range of serum alkaline phosphatase values.

On the basis of the phosphatase values on the one hand and the severity of the rickets (as revealed by the clinical and roentgenographic findings) on the other, the cases fell into certain groups. On admission in the clinically mild cases the values were roughly 20 to 30 units, in the moderately severe cases up to 60 units, and in the very severe cases above 60 units and up to 190 units. Thus there was, on the whole, a definitely positive correlation between the severity of the clinical condition on the one hand and the degree of alkaline phosphatase activity of the serum on the other. In harmony with this correlation, many of the cases admitted merely for correction of rachitic deformities yielded normal phosphatase values, and clinical and roentgenographic examination showed that the rickets was healed, irrespective of the immediate external impression which these cases may have created.

It is interesting also to examine the serum calcium and inorganic phosphate values on admission in relation to the corresponding phosphatase values. The serum calcium value was not ascertained in all cases, but of those in which it was, about one-third showed a definite hypocalcemia (less than 9 mg.), one-third a suggestion of hypocalcemia (9 to 10 mg.), and one-third no hypocalcemia (10 to 10.7 mg.). However, there was no reliable correlation between serum calcium and the severity of the rickets in the different cases on admission. On the other hand, the serum inorganic phosphate value, while known to be a much more reliable index of the severity of rickets than the serum calcium, was still not as uniformly reliable as the serum phosphatase value. Though a distinct depression of the inorganic phosphate level to 3 mg. or less was associated in general with the higher phosphatase values (at least 50 or 60 units), some high phosphatase values were found also with inorganic phosphate values between 3 and 4 mg. or even higher.

Altogether, the alkaline phosphatase value is not only a good index of the severity of the rickets but usually also a better guide to the adequacy of the antirachitic treatment and a more accurate indication of the complete abolition of the rachitic state than the calcium value or even the phosphorus value. Specifically, the inorganic phosphate is likely to rise promptly even under somewhat inadequate treatment. The phosphatase value drops decidedly only when the antirachitic treatment is adequate, and does not reach the normal level in its fall until the healing of the rickets is really complete.

Hyperparathyroidism: In 15 cases of so-called primary hyperparathyroidism we obtained initial alkaline phosphatase values ranging from 4.5 to 35 units—that is, from just above the upper limit of the normal to over twelve times the normal average. In these cases, there was a rough positive relation between the level of the phosphatase value and the severity of the skeletal alterations as ascertained roentgenographically. Indeed, in two cases in which the initial values were 4.5 and 4.6 respectively, osseous changes were so inconspicuous that they could easily be overlooked roentgenographically. The first of these two cases was followed for 15 months before the offending parathyroid tissue was removed. During this time, the phosphatase value rose from 4.5 to 7.6 units, and concomitantly one could observe some increase in the bone changes detectable roentgenographically.

After removal of the offending parathyroid tissue in a case of hyperparathyroidism, the less elevated the pre-operative phosphatase value has been (and accordingly the less pronounced the skeletal alterations) the more rapidly does the value drop to the normal level. Thus, in the case just mentioned, in which the phosphatase value had risen only to 7.6, only five months elapsed before it was down to the normal level of 2.7. On the other hand, in a case in which the pre-operative phosphatase value was 23 units (and in which incidentally the bone changes were very severe) it was only in the course of 3 years that the phosphatase value finally came down to the distinctly normal level of 2.2 units. The return of the phosphatase value to a normal level signifies that recalcification of the skeleton has been completed.

In cases of secondary (renal) hyperparathyroidism the serum alkaline phosphatase values parallel those seen in primary hyperparathyroidism, in accordance with the severity of the bone changes. In one of several cases which we studied, the initial phosphatase value was 23

units. Accordingly, in this case, the patient, an adult, showed osseous changes which were quite pronounced roentgenographically. It may also be worth noting in this connection that they were indistinguishable from changes to be observed roentgenographically in a correspondingly severe case of primary hyperparathyroidism. Indeed, anatomically too, the osseous changes of primary and secondary hyperparathyroidism in adults are indistinguishable.

Osteomalacia: In three instances of a rare type of non-puerperal bone-softening in adults, which represents this country's closest approximation to genuine osteomalacia, the serum alkaline phosphatase values were 10.3, 11.1, and 13.5 units respectively. In these cases, the serum calcium and inorganic phosphate values were low, as they are in genuine osteomalacia. One of these cases came to autopsy, and the bone changes found could not be differentiated anatomically from those of genuine osteomalacia. Nevertheless, this case, like the other two cases, is puzzling in that it was refractory to the usual treatment for osteomalacia (that is, a high calcium diet and a high vitamin D intake).

Non-Tropical Sprue: In three instances of non-tropical sprue in adults, the serum alkaline phosphatase values were 5.6, 8.2, and 10.8 units respectively. Furthermore, these cases all presented pronounced hypocalcemia and mild hypophosphatemia. In all 3 instances, the bones were more or less porotic.

One must point out, however, that in cases of menopausal osteoporosis much more pronounced and indeed devastatingly severe osteoporosis may occur and yet the phosphatase, calcium, and inorganic phosphate levels all remain within normal limits. Perhaps the osteoporosis in these cases represents an exaggerated manifestation, in the skeleton, of the post-menopausal involutional processes going on in the body as a whole. Indeed, in merely senile osteoporosis the phosphatase, calcium, and inorganic phosphate values of the serum are usually also not abnormal, although again the bone thinning may be very pronounced.

Osteogenic Sarcoma: At first admission for treatment, a case of osteogenic sarcoma may or may not show an elevation of the alkaline phosphatase value. Of the eleven cases tabulated in Table 1, there are four in which the value could legitimately be regarded as definitely above normal for the age of the patient. In two, it might be regarded as just above the normal (age 18—4.3 units; age 26—4.1 units). Furthermore, it appears to us from the data in this table (though the series is small)

TABLE I

OSTEOGENIC SARCOMA
(Values on Admission)

Age	*Alk # E*	*Site*	*Follow Up*	*Age*	*Alk # E*	*Site*	*Follow Up*
10	7.7	F.	Died 16 mo.	26	4.1	H.	Alive 10 mo.
13	42.4	F.	Died 6 mo.	32	3.0	H.	Died 6 mo.
15	6.1	F.	None	42	16.6	F.*	None
16	4.1	F.	Alive 1 yr.	44	2.7	F.†	Died 4 mo.
18	4.3	I.	None	53	22 8	F.	Died 8 mo.
21	9.3	F.	Died 2 yr.	F.—Femur; H.—Humerus; I.—Ilium.			

* Pulmonary metastases.
† Pul. metastases suspected.
# E = Phosphatase.

that the initial phosphatase value offers no indication of the relative rapidity with which death will ensue. (In our experience, survival periods of more than 2 years from the time of admission are rare in any event in unequivocal cases of osteogenic sarcoma).

Post-amputation follow-up studies in some of these cases showed in the first place that when the phosphatase value had been distinctly high, it promptly dropped, sometimes even to a level normal for the age of the subject. Furthermore, there was not necessarily a distinct rise from this level when metastases were first manifest roentgenographically. However, subsequent values, especially if obtained only a few weeks or months before death, were always well above the normal, and in one case reached 94 units.

Other Tumors Primary in the Skeleton: Conditions such as giant-cell tumor, benign chondroblastoma, solitary benign enchondroma, chondrosarcoma (not much calcified or ossified), and solitary osteochondroma never elevate the alkaline phosphatase value of the serum. Ewing sarcoma does not do so either, even after it has become widely disseminated through the bones of the body, provided that there are no significant metastases to the liver. Of our seven cases of multiple myeloma, there were six in which the phosphatase values were strictly within the normal limits for adults, ranging between 1.8 and 3.5 units.

In the remaining case, the initial and subsequent alkaline phosphatase values were somewhat elevated. In this case (confirmed by autopsy) 20 determinations were made in the course of a year, and the values were always found above normal. The value was 5.1 on initial examination, reached a peak of 9.7 within 2 months, dropped irregularly during the subsequent 9 months to 4.2, and rose again to 6.4 shortly before death. In the liver, only one metastatic lesion, 0.5 cm. in diameter, was discovered, and this would hardly suffice to explain the increased phosphatase value in this one case, which has been more fully discussed elsewhere.[12]

Tumors Metastatic to the Skeleton: Unless these provoke bone formation—that is, unless they are osteoplastic—they do not tend to raise the alkaline phosphatase value. Thus, in a case of carcinosis in which the skeletal metastases are extensive but solely osteolytic (and by chance the liver is spared) the alkaline phosphatase value would theoretically be normal, or at most very slightly increased by the effects of callus formation around fractures. If on subsequent examination in such a case the alkaline phosphatase value was found to have risen say to 10, 15 or 25 units, one could prognosticate that autopsy would certainly reveal more or less extensive metastases to the liver, even in the absence of clinical jaundice or an increase in the serum bilirubin.

As to the cases presenting osteoplastic metastases (including cases of prostatic carcinoma—see also below) these are associated with definite though not necessarily dramatic rises in the alkaline phosphatase value. Specifically, in these cases, in the absence of metastases to the liver, the alkaline phosphatase is often not elevated to above 8, 10, or 15 units, even if the extent of the osteoplastic metastases is considerable. However, in one case (that of a woman of 37) the alkaline phosphatase value rose during the month before death, from about 56 units to 85 units. Autopsy revealed that the carcinoma was primary in a bronchus, while the liver contained only a few pinhead-sized metastases, so that the dramatically high values in this case can safely be ascribed almost solely to the osteoplastic metastases, which involved nearly the entire skeleton.

Systematized Anomalies of Skeletal Development: Among these, one is quite likely to find a definite elevation of the alkaline phosphatase value in fibrous dysplasia of bone[13] (if the extent of the skeletal involvement is considerable). In two such cases, we obtained values of 17.1 and 22.6 units respectively. Sometimes these cases are mistaken clinically for instances of hyperparathyroidism, but aside from clear-cut clinical

differences between these two conditions it may be pointed out that in fibrous dysplasia of bone the calcium and inorganic phosphate values of the serum are within normal limits. In cases of osteopetrosis (marble bone disease) the phosphatase value may likewise be increased. In one case—that of a boy of 16—the value on admission was 21.3 units. In cases of osteogenesis imperfecta the value may be found raised above the normal for the age of the subject if fractures are present. In none of a number of cases of multiple exostosis, skeletal enchondromatosis, and achondroplasia did we find elevations of the alkaline phosphatase value of the serum.

Significance of Increased Alkaline Phosphatase Values in Skeletal Disease

After this survey of the various skeletal disorders showing increases in the serum alkaline phosphatase value, it seems appropriate to crystallize and restate the common factor apparently underlying the elevation. This factor seems to be the new formation of some kind of osseous tissue in connection with the disorder.

On the basis of this idea, one can understand why the serum alkaline phosphatase value should be particularly high when there is extensive Paget's disease, since in that disease the reactive formation of new bone is unusually lively, although the osseous tissue formed is not normal. On the same general basis, one can understand why this value is particularly high in moderate or severe rickets, even though in this disorder the osteogenic reaction is expressed in the formation only of osteoid and not of true bone. Again, in hyperparathyroidism the demineralization of the bones is associated with reactive scarring and new bone formation, and accordingly with a rise in the phosphatase value. On the other hand, in uncomplicated cases of senile osteoporosis and menopausal osteoporosis, in which even devastatingly severe thinning of the bones is usually not associated with reparative new bone formation, the phosphatase value tends to remain at normal levels. Correspondingly, in those tumorous disorders in which the skeletal lesions are purely lytic (multiple myeloma, for instance) the phosphatase value is usually also not above normal. In those tumorous disorders in which the skeletal lesions are osteoplastic (osteogenic sarcoma, osteoplastic carcinomatous metastases) the phosphatase value is likely to be raised.

Altogether, these examples seem to suffice to show that the new

TABLE II

CASES NOT CARCINOMA OF PROSTATE AND SHOWING HIGH ALKALINE E VALUES

No.	*Acid # E*	*Alk # E*	*No.*	*Acid # E*	*Alk # E*
1	0.2	7.0*	6	0.1	18.3*
2	0.3	10.4‡	7	0.4	25.6‡
3	0.5	12.0‡	8	0.3	27.2†
4	0.3	14.9*	9	0.6	94**
5	0.3	16.0‡	10	0.5	121*

* Paget's disease.
† Cirrhosis of liver.
‡ Carcinoma with extensive metastases.
** Osteogenic sarcoma with extensive metastases.
# E = Phosphatase.

formation of osseous tissue in connection with skeletal disorders is the factor positively correlated with the rise in the alkaline phosphatase value. Corroboratively, the healing of a skeletal disorder (for instance rickets or hyperparathyroidism) through appropriate therapy is associated with a decline of the phosphatase value to the normal level, in harmony with the cessation of the abnormal reactive osteogenesis.

RANGE OF VALUES FOR SERUM ACID PHOSPHATASE

As determined by the Bodansky method, the normal range of serum acid phosphatase values (for children and adults of both sexes) can be stated as lying between 0.1 and 0.4 units per 100 cc. As determined by the Gutman method, the corresponding values are 0.5 and 2.5 units.[1] About 90 per cent of hospitalized subjects without prostatic disease show values within the indicated normal ranges by both methods. Values above 0.8 units by the Bodansky method and 10.0 units by the Gutman method must be regarded as definitely abnormal and specifically as indicating the presence of prostatic carcinoma which has metastasized.

The values falling within the intermediary or doubtful zone (0.4 to 0.8 units and 3.0 to 10.0 units respectively by the two methods) raise some questions. First of all, as shown by Table II, acid phosphatase values* within this range are obtained not infrequently in cases showing

* From this point on, unless otherwise indicated, the values will be given in terms of Bodansky units only.

TABLE III

BENIGN HYPERTROPHY OF PROSTATE

Age	*Acid # E*	*Alk # E*	*Age*	*Acid E*	*Alk E*
67	0.1*	3.3	70	0.3	5.5†
57	0.2	3.6	78	0.3	1.9
63	0.2*	2.0	63	0.4*	2.3
82	0.2	2.9	63	0.4*	2.1
65	0.2	4.8	76	0.7*	..

* Tissue examination showed fibroadenomatous hyperplasia. # E = Phosphatase.
† Osteoporosis due to nutritional deficiency.

TABLE IV

CASES OF PROSTATIC CARCINOMA WITHOUT OR BEFORE ORCHIECTOMY

Case No.	*Acid # E*	*Alk # E*	*Metastases by x-ray*	*Case No.*	*Acid # E*	*Alk # E*	*Metastases by x-ray*
1	0.3	2.9	Absent	6	1.0	4.1	Absent†
2	0.4	6.7	.....	7	2.6	12.3	Present
3	0.7	3.3	Absent	8	3.3	4.1	.....
4	0.8	8.8	Present*	9	12.8	14.6	Present
5	0.8	9.1	.....	10	30.2	8.5	Present

* Negative 3 months before this value was obtained (at which time the alkaline E was 2.3 u.) but positive 4 months after it was obtained.
† Clinically, the tumor had already extended to the periprostatic soft tissues.
# E = Phosphatase.

high alkaline phosphatase values and not representing carcinoma of the prostate. Indeed, three of the ten cases shown in this table had values falling within the doubtful range and specifically of 0.5, 0.6, and 0.5 units respectively. Values within the doubtful range are also obtained in similar cases by the Gutman method. Furthermore, in our experience, an occasional instance of benign hypertrophy of the prostate may also yield values within this range, as shown in Table III. Finally, it must be pointed out that, as shown by Table IV, some proved cases of carcinoma of the prostate show acid phosphatase values not only within the doubt-

ful, but even within the normal range. In this respect, also, our experience is in harmony with that of others.

Serum Acid Phosphatase Values in Cases of Prostatic Carcinoma

Table IV shows data on ten cases of unequivocal carcinoma of the prostate without orchiectomy or before orchiectomy. The cases are arranged in increasing order of the acid phosphatase values. In the first two of these cases, these values are within our normal range. In the third case the value (0.7) is in the doubtful range. In the other seven, it is in the abnormal range, reaching, in one case, the extreme value of 30.2 units (roughly 100 times the normal average).

In regard to five of these last seven cases, we have data as to whether or not metastasis was present roentgenographically in the pelvis and neighboring bones. In the four in which we know it was present, the high acid phosphatase value was associated with some rise in the alkaline phosphatase value. In the fifth case, in which we know it was not present, the surgeon (Dr. Paul Aschner) informs us that clinically the tumor, while already metastatic, had apparently extended only to the periprostatic soft tissues. In this case, the alkaline phosphatase value (4.1 units) was at the upper limit of the normal. Thus, these cases confirm, in the first place, what has already been established by Gutman, by Barringer and Woodard,[14] by Huggins and Hodges,[15] and by others on the basis of much larger series—namely, that when the carcinoma breaks the bounds of the prostate and metastasizes to the regional tissues and to the skeleton, the acid phosphatase value of the serum usually rises to an abnormal level. This rise is due to the fact that the acid phosphatase secreted by the prostatic tumor tissue is entering the circulation in large amounts. Furthermore, these cases show again that the osteoplastic response of the skeletal tissues to the metastases is the factor responsible for the rise in the alkaline phosphatase value of the serum. On the other hand, these conclusions are corroborated by the findings in our cases showing low or only doubtfully elevated acid phosphatase values. In only two of our three cases of this kind do we have roentgenographic data on the presence or absence of metastases. However, in both of these, skeletal metastases were absent, and in both again the alkaline phosphatase level was within normal limits.

Table V presents a series of acid and alkaline phosphatase determinations in a case of carcinoma of the prostate in which both of these values

TABLE V

CASE OF CARCINOMA OF PROSTATE TREATED BY ORCHIECTOMY

Date	*Acid # E*	*Alk # E*	*Date*	*Acid # E*	*Alk # E*
3/12/41	2.6*	12 3	4/ 7	0.1	3.7
6/30	Orchiectomy		6/30	0.4	3.4
8/ 1	..	19.5	11/ 8	1.2	6 4
11/ 5	0.5	5.2	1/11/43	1.4	12.6
12/ 3	0.4	3.4	3/19	1.0	14.6
1/ 5/42	0.3	3.2	4/ 5	1.1	17.6

* Metastases to skeleton apparent in x-ray films.
# E = Phosphatase.

were high and metastases to the skeleton were already apparent in the x-ray films before performance of a therapeutic orchiectomy. This case has been followed for 21 months after orchiectomy. Though unfortunately we lack, in this case, an acid phosphatase determination to go with the first alkaline phosphatase determination after orchiectomy, yet the data illustrate the usual postoperative course of these values in such cases and are particularly valuable on account of the long period covered. Postoperatively (as we know from other cases) the acid phosphatase starts to decline sharply, and concomitantly the alkaline phosphatase rises. The latter then also starts to decline. In the case shown in the table, 8 months postoperatively, the acid and alkaline values had both gone down to normal (0.1 and 3.7 units respectively). Some months later, however, they had both begun to rise again—the acid value first and even more steeply than the alkaline—and on the last examination—21 months after the operation—the acid value was 1.1 units and the alkaline 17.6 units.

In connection with the course of the phosphatase values in this case, the course of the changes in the roentgenographic findings is interesting. The immediate postoperative rise in the alkaline phosphatase value was associated with a prompt increase in the osteoplastic reaction to the metastases in the pelvic bones. Specifically, areas which previously had not appeared osteoplastic roentgenographically soon did appear so, the pelvic bones having become much more extensively radiopaque than

they had previously been. Some months later, when the acid and alkaline phosphatase values had dropped to normal levels, the roentgenogram showed substantial decrease in the radiopacity of the pelvic bones. Again some months later, with the return of the acid and alkaline phosphatase to high abnormal values, the pelvic bones are again showing pronounced and extensive opacity roentgenographically.

It is not possible to be certain about the explanation of this series of changes in the postoperative roentgenographic pictures. It may be surmised that the immediate effect of the orchiectomy upon the tumor tissue proper in the pelvic bones was to arrest its growth, and that this arrest was associated with an osteoplastic reaction tending to crowd out the tumor tissue more completely. After the metastatic tumor tissue had become more or less choked off in consequence, the osteoplastic reaction tissue apparently began to be resolved. Subsequently, the checking influence of the orchiectomy upon the residual tumor tissue in the pelvic bones would seem to have weakened, and, in association with the consequent regrowth of the tumor tissue, there was an intensification of the osteoplastic reaction to it.*

* This patient, who was on the urological service of Dr. Paul Aschner, and on whom Dr. Isidor Palais did the orchiectomy, has since died and come to autopsy. Death occurred on June 14, 1943, 23½ months after the orchiectomy. It may be profitable to summarize the total picture which has thus now become available. Concomitantly with the return of the alkaline and acid values to within the normal range after the orchiectomy, there was a pronounced improvement in the general and local clinical status. Indeed, in regard to the latter, whereas prior to orchiectomy the tumorous prostate was very large and hard, eight months after it, Dr. Aschner noted that the right lobe was of normal size while the left lobe was also small though it was nodular at its apex. Concomitantly with the subsequent new rise in the acid and alkaline phosphatase values to abnormally high levels there was a definite and rapidly progressive recurrence of the prostatic enlargement. The patient was readmitted to the hospital on May 5, 1943, at which time a large boggy mass was found on the floor of the pelvis, surrounding the rectum. On May 11th, the acid phosphatase value was 1.8 and the alkaline phosphatase value 43 units.

At autopsy it was found that the local pelvic tumor mass, in which the prostate could no longer be distinguished as such, had infiltrated the floor of the bladder, the space of Retzius, and the peri-rectal tissues and had produced a so-called "frozen pelvis." Section of this tumor tissue showed it to be a highly anaplastic carcinoma. Tumor tissue was found nowhere else except in the skeleton, which was heavily involved. The metastases to the skeleton were all osteoplastic. It is worth noting that histologic examination of the bones indicated that, in the past, metastatic tumor tissue in them had undergone widespread necrosis. However, in addition to wide areas of necrotic tumor the sections also revealed a good deal of viable and actively growing carcinomatous tissue in the bones also. It would seem that one of the deductions which can be made from the histologic appearances in the bones is that one of the immediate direct or indirect effects of orchiectomy is necrosis of the metastatic tumor tissue, reflected in turn by a sharp drop in the acid phosphatase value. The postoperative reduction in the size of the prostate may likewise be an expression of tumor necrosis and secondary tumor resolution. The subsequent reactivation of the tumor growth, both locally and in the bone, is, of course, the basis for the new rise in the acid phosphatase values.

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LONG CALDERWOOD

The Birthplace of the Hunters

FENWICK BEEKMAN

BEING present in the City of Glasgow during the latter part of the spring of 1935, the author decided to visit the birthplace of William and John Hunter at Long Calderwood, an old farmstead situated but a short distance from the kirktown of East Kilbride, in Lanarkshire. The June day was warm and overcast and light showers of rain, ceasing as abruptly as they commenced, repeatedy obliterated the landscape with a curtain of film, to be followed by bright sunshine.

Starting early in the afternoon, our motorcar carried us across the Clyde by way of the new George V Bridge and thence through the old streets of what was formerly the town of Gorbells. The road then led us along the south bank of the river to Rutherglen, passing on its way the Glasgow Green upon the farther bank. Reaching Rutherglen, the highway turned toward the south and rapidly ascended some five hundred feet of the slope of the Clyde Valley to reach the brow of Dychmont Hill. Here an extensive view is obtained, not only of the Clyde and the City of Glasgow, but also, on a clear day, of Arthur's Seat in the suburbs of Edinburgh, Ben Lomond and the Peaks of Arran. Traveling a mile farther, the kirktown of East Kilbride was reached.

East Kilbride, seven and a half miles south of the City of Glasgow, is built upon the northeasterly edge of a richly cultivated plateau, stretching southward into the shires of Ayr and Dumfries. To the north and east, the land dips gently into the winding valley of the Clyde, on the banks of which, five miles distant to the east, stands the City of Hamilton. The surface of the surrounding country, with its rolling hills and dales, is rudely broken here and there by rugged, stony "craigs," which rise high above the fields. The land is fertile and green, for it is used for the pasture of sheep and cattle, or the cultivation of grain. Much of the old kirktown appears to remain in the same state it was two hundred years ago, except perhaps for a few modern cottages that have been erected here and there. On the eastern and southern sides of

Fig. 1. Church at East Kilbride.

Fig. 2. Grave of John Hunter, Sr. and wife, Agnes Paul—(Flat stone, center).

a central square stand two rows of old stone-fronted buildings with gabled windows in the roofs and doorways opening directly upon the roadway. One of these buildings is said to have been the inn; the others may have contained stores with living apartments above. A narrow passage, paved with flagstone and nearly hidden from view between the two rows of buildings, leads the visitor directly to the "auld kirk," standing upon the brow of a small hill, its burying ground stretching gently down toward the east (Figure 1). The church, a simple, rec-

tangular, stone building with a slate roof sloping up from its four walls, has a square clock tower built against its north wall, which is surmounted by a Gothic crown or lantern which in design is much like that upon the tower of St. Giles' Cathedral in Edinburgh. The well-kept burying ground, surrounded by a stone wall with iron gates guarding the two entrances, contains ancient gravestones and a "watchers' house," where vigil was kept against the marauding of "resurrection men." Close to the east wall of the kirk, lies a flat, brownstone slab (Figure 2). The carved inscription upon its weather-beaten surface, though dulled by age and filled with lichen, can still be read.

THIS IS THE BURIE
ALL PLACE OF IOHN
HUNTER OF CADER
FEILD* AND AGNES PA
UL HIS SPOUSE
1751

This John Hunter, grain merchant of East Kilbride, was born during the early years of the reign of Charles II, probably in the year 1663, and on December 30th, 1707—at the age of forty-four—married Agnes Paul, a handsome, talented lass twenty-two years his junior, the daughter of Baillie John Paul, a malster of the City of Glasgow. John Hunter took his bride to East Kilbride where they lived for ten years, during which time she bore him six children. At the age of fifty-four, John Hunter reached the important decision to withdraw from the laborious business of merchant and retire to what he thought would be the more leisurely life of a farmer. He therefore purchased a farm, it is said for the sum of £147, upon which he built a modest dwelling. To this simple home he moved with his wife and four children, for two of the six children born in East Kilbride had died during their infancy.

Entering our motor again, we left the kirktown behind and traveled northeast along Hunter Street, an old country lane bordered with thick hedges. Long Calderwood, the house that John Hunter built for his family, is approximately one mile distant from East Kilbride. The visitor, as he approaches, easily recognizes the homestead from some distance, almost hidden by trees, situated on the left hand side of a gentle

* The use of Calderfield instead of Calderwood is explained by Mather as follows: "the parish was then divided into townships, hamlets or clachans; Calderfield being the name of the township, and Calderwood the biggest house in it, the whole came to be recognized by the latter name."

curve in the roadway as it turns to the east toward Blantyre, on its winding way to Hamilton, five miles distant. The original dwelling has been, without a doubt, slightly altered, but the farm buildings appear to have been added to extensively during the two centuries that have elapsed since the "laird" of Long Calderwood first erected his farmstead.

William Hunter inherited Long Calderwood upon the death of his brother James, in the year 1745, and added to its acreage. In a letter to his friend William Cullen, on August 6th, 1754, he wrote: "I know you'll say *another letter from Hunter! What the devil is he about now?* Why, I am going to buy land: the first time this has ever entered into my head. In short, Mr. Fleming of Nook, in Kilbryde, writes me that Mr. Borland is going forthwith to sell his land in Longcalderwood. It lies contiguous, you know, to what was my father's and the two together make a vote in the county. If I could get it, both would be as easily managed as one, and should it afterwards be expedient, both might be sold with the same trouble as one. Besides, I cannot get it out of my head that I shall one time or other live there, and, in that case, I should like to possess both, that I might have a little bit all around me that I could call my own, and to give you a vote, or any of your friends that should stand for the county member." Though the owner of Long Calderwood for thirty-eight years, William Hunter, it seems, found the opportunity of visiting it only once, in 1750, just before his mother's death. At present "the estate," Sir Arthur Keith informs us, "comprises 177 acres." William Hunter willed the property to his nephew, Matthew Baillie, on his death in the year 1783, having become estranged from his brother John. Baillie, however, recognizing the injustice of this act, deeded the property over to his younger uncle. John Hunter owned Long Calderwood for ten years but never visited it during this time and, when he died in the year 1793, the farmstead returned again to Matthew Baillie. Since then it has been continuously in the Baillie family and this may well account for the excellent condition in which the old farmstead is found today.

John Hunter, Sr., built his house facing the south, on the north side of the road, the rear overlooking cultivated fields that stretch toward the valley of the Clyde. The house and connecting farm building (Figure 3), substantially built of roughly hewn stone, but now stuccoed,*

* A photograph of the homestead, taken by Annan of Glasgow in the year 1885, portrays the house and connecting building before the walls were stuccoed.

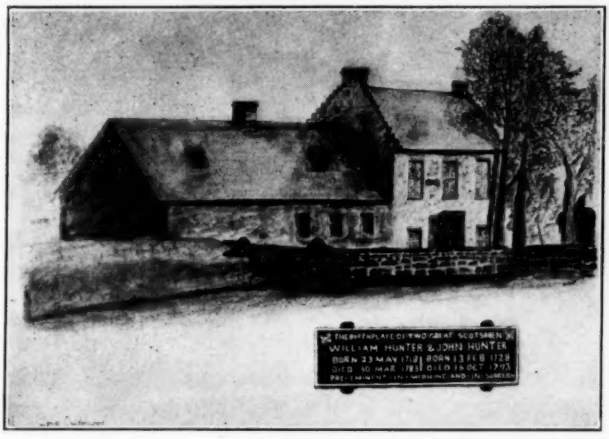

Fig. 3. Long Calderwood (Author's pencil sketch).

are separated from the road by a narrow strip of terraced lawn behind a low stone wall. The dwelling portion, two stories high, is square in shape, with gabled ends that rise above the level of the roof and are cut with corbie-steps leading up to square, squat chimneys placed at either end of the peak of the slated roof, which may be assumed to have replaced one of thatch. The long, low farm building, in size out of all proportion to the dwelling, extends from the west gable forming, with other stone out-buildings, a farmyard in the rear. This is entered from the highway by a wagon road, spanned by stone gate-posts, to the west of the farm-building. "The long low stone building which abuts on the western gable of the house," writes Sir Arthur Keith, "provides a scullery, a 'bothy' and stabling for five horses, is clearly of later date; so is the small coach-house and great cow-byre behind the dwelling-house. But the barn, with its loop-holed and slotted end towards the road, its doorways on opposite walls, between which the corn was threshed by flail and winnowed by hand—is certainly part of the farm-steading which John Hunter's father built."

The front of the dwelling has three large windows, giving sunlight to the bedrooms on the upper floor; while the main entrance, a narrow doorway within a small porch, reached by two stone steps, with a window on either side, opens upon the ground floor. A tablet, more recently placed upon the wall to the right of the porch and on the level

of the upper windowsills, commemorates the birth in this humble home of the two illustrious Scotsmen.

The visitor, on entering the dwelling, finds himself within a narrow passage running from left to right. Directly in front of him, ascending to the left, is a narrow stone stairway leading to the floor above. To the left is the kitchen, a room some fourteen feet square, with a door opening into the "bothy," where the farm help slept, and containing a spacious fireplace, once holding crane and spit but now occupied by a common cook-stove. To the right the passageway gives entrance to a room of much the same dimensions as the kitchen, with a window opening to the south and another to the east. Though now a parlor, an alcove with sliding panels built against the north wall and containing two beds denotes that the room was used at one time as a sleeping apartment. Behind the stairway and between this room and the kitchen, is a third, little larger than a closet, that was probably used as a chamber for one or more of the numerous children of the family. The upper floor is laid out in like plan to that below. The chamber above the kitchen is said to have been occupied by the parents and here the four youngest of the family, it is assumed, were born.

The four children, brought to Long Calderwood by their parents in the year 1717, were John age nine, Janet age four, James age two, and Agnes age one. Less than a year after taking residence on the farm, their seventh child and fourth son was born, on May 23rd, 1718, and was named William. Dorothy was born January 26th, 1721 and, a year later, their eldest child, John, died on February 27th, 1722. Isabel was born December 7th, 1725 and finally two years later, on February 14th,* 1728, the last-born of the aging couple arrived and was named John.

At the time of this important event John Hunter, Sr. was at least sixty-five years of age and his wife forty-three. Besides the infant "Jock," there were six other children, Janet the eldest being fifteen years of age, James thirteen, Agnes twelve, William ten, Dorothy seven and Isabel two. It was a happy family, the children having an intense devotion for their parents, especially their mother, as well as for each other. Mrs. Hunter was an outstanding woman of strong character, if

* There has been considerable discussion as to the exact date of John Hunter's birth. Drewry Ottley states that John Hunter used February 14th for his birthday and the Royal College of Surgeons (Eng.) has chosen this day for the celebration of the anniversary of his birth. The parish register at East Kilbride gives February 13th, 1728 as the day of his birth and his baptism on March 30th. An old Bible, formerly the property of James Hunter, puts the date as February 7th and a contemporary notebook, formerly owned by Miss Hunter Baillie, states that John was born on the 9th. Everard Home gives the date as July 14th; this, however, must have been a typographical error. Stephen Paget says, "Probably he was born during the night of the 13th-14th."

we can judge from the little that is known of her, possessing deep affection, lasting patience, and untiring will and a great deal of common sense. During her youth in Glasgow, Agnes Paul had received an excellent schooling and had acquired many of the lady-like accomplishments of the time, for she was the daughter of a man of means and of importance in the community, who was not only a Magistrate but also held the honorary office of Treasurer of the City. Her married life had been hard, for it was no easy task to bear ten children, to care for them, keep house and assist at the dairy work on the farm. Her ambition for her children's careers, however, does not appear to have been dampened by the hard work and many worries which we shall see were ever present, for it seems she found time to train them in polite manners, gentlemanly and ladylike customs, as well as the accomplishments that she had acquired during her younger days. The "laird," John Hunter, Sr., appears to have been a man of intelligence, patience and industry, who had in all probability received a grammar school education and possessed at least a desire for some of the cultural pursuits. Observing his portrait, painted about the year 1740 by his son, James, shortly before his death, which now hangs in the halls of the Royal College of Surgeons (Eng.), we perceive an old man. The features of his smooth-shaven face, though clean-cut and full of character, appear careworn. The mouth, with thin, tightly closed lips and prominent jaw, denotes determination and the eyes, though kindly, possess a peculiar, piercing quality that commands respect. His grandson, Matthew Baillie, said "he was a man of good understanding, of great integrity and of an anxious temper."

The life on this small farm was in all probability a busy one, for neither of the parents were shiftless and there was little if any money to spare for hiring help on the farm or in the house. It may be presumed that "Jamie" and "Willie," when not attending the grammar school at East Kilbride, were called upon to assist their father in the fields or tending the herd. Janet was certainly mature enough to relieve her mother of some of the house and dairy work and "Nannie" (Agnes) no doubt was intrusted with the care of her two little sisters "Dollie" (Dorothy) and "Tibbie" (Isabel) and perhaps with baby "Jock." There is no doubt that "Jockie" was pampered, petted and indulged in all his childish fancies, by his mother and four sisters, from the time of his birth; and shortly, as we shall see, he was deprived of the companionship

of his elder brothers, whose presence might have strongly influenced his early training and thereby counteracted the coddling of the feminine members of the family.

Mr. Hunter appears to have desired that his sons should not enter "trade" as he had done and, consequently, planned to educate the two older ones, who were now finishing grammar school, where they had shown exceptional ability, for professional lives. In order to accomplish this, further sacrifices had to be made by the parents. We find that the herd boy was dispensed with a year before "Jockie's" birth and a year after fifteen acres of land were sold in order, it is said, to settle the payment on an indenture, to a writer of the Signet in Edinburgh, for "Jamie," who was now fourteen years of age, was to study law. Two years later, in the autumn of the year 1731, "Willie," now thirteen years of age, a small, slender lad, frail in frame with delicate features much like those of his father, entered the "College" at Glasgow to study for the ministry in the Scotch Kirk; having obtained a bursary of the Bajan* Class to the amount of £10 per annum for four years, although the curriculum required for graduation called for five years attendance.

Coming under the influence of that great secular scholar, Francis Hutcheson (1694-1746), who held the Chair of Moral Philosophy, William Hunter soon developed a spirit of scepticism about what he was taught and a desire to learn through inquiry. Buckle, in his *History of Civilization in England*, writes that: "By his lectures, and by his works, he [Hutcheson] diffused a taste for bold inquiries into subjects of the deepest importance, but concerning which it had previously been supposed nothing fresh was to be learned; the Scotch having hitherto been taught, that all truths respecting our own nature, which were essential to be known had been already revealed." Having finished his five years of study, William discovered that he was unsuited for the ministry and declined the office in the Church and, in consequence, did not receive a degree.

Returning home in the summer of 1736, he joined a young practitioner at Hamilton, a friend of the family, named William Cullen (1710-1790), as an assistant. A lasting friendship ensued and later in life William Hunter often acknowledged that these "were the happiest years of my life." Residing with Cullen until the autumn of 1739,

* Mather informs us that "The term Bajan was employed in the French and Scotch Universities, and is evidently a corruption of *bec jaune* (yellow beak), an expression meant to designate a nestling or unfledged bird.

William Hunter then went to Edinburgh in order to attend the lectures of Alexander Monro on anatomy, and in the following year he sailed from Leith for London, in order to obtain further study in preparation for undertaking the surgical part of the practice, as a partner of William Cullen at Hamilton.

During William Hunter's absence, the tranquility of Long Calderwood was rudely interrupted by a series of unhappy events, that have been dramatically chronicled in intimate letters addressed to him in London. These reveal the deep affection that existed between the members of this humble family, residing on the small farm in Scotland, and gives us a glimpse of their stalwart characters and simple faith in God. The first of the letters vividly pictures the poignant grief occasioned by the untimely death of Agnes, a favorite sister but particularly dear to the elder brother James, the author of this pathetic epistle. Her death occurred on March 13th, 1741, while away from home, accompanying her brother James who had taken his sister with him to a neighboring town where he was to exchange a farm horse. Mounted behind her brother, though weakened by the ravages of pulmonary tuberculosis, "Nannie" and "Jamie" set forth upon their fateful journey; but before traveling far on their way, the brother realized that all was not well. In his narrative to William, he wrote: "we no sooner allighted from our horse when she complained of a faintness great weakness and cold feet: with the little assistance I could give her she sat there pretty easy for 2 hours, we mounted our horse again for Hamilton, . . ., but before we had got the length of a Gun shot away, she grew so weak that I was obliged to turn back, after giving orders to the Good wife about her I rode to Hamilton post haste and brought Dr. Cullen out with me, by this time she had got to bed and was tolerably easy but extreamly weak, . . ., we got a Car and put a bed upon it, and he took her in his arms and lay[d] her gently down upon it, it put me in mind of the poets bringing Eleonora into the Sun to take her last sight and farewell of the world, she was no sooner laid down but she complains of her faintness occasioned by the fatigue of coming out. Mr. Cullen found she could not make it out, takes her up again in his arms to carry her in, there she resigned her young and tender soul. I was thunderstruck with such an unexpected mournful sight, nor will I ever forget that approving nod she gave me the moment she dyed. I gave myself up to the most violent grief which I had all along stiffled upon her account, and the Doctor,

instead of comforting me, had me indulge it to the utmost. . . ."

"I would not advise you to stiffle your grief, no, my dear Will, indulge it heartily, give it the loosest reins the more impetuous it is, the better 'twill sooner satiate itself. . . . When I cast my eye upon that Blanck made be (wixt) you and me, which but a little while agoe our dear sister filled, methinks it looks a gloomy dismall vacuum." And in closing his letter he wrote: "Take care of your health my Dr. Willie, forget not to pray to Nannie, imagine you have a sister in Heaven who is as able, I hope, as willing to hear and do for her friends here; . . .

Three months later William Hunter, having received an offer to become the assistant of Dr. James Douglas (1675-1742), made up his mind to remain for an indefinite period in London. The news of this decision appears to have precipitated considerable consternation within the family at home, as revealed through the contents of a letter written to "William" by his aging father, dated 28th July 1741:

"Nothing has proved a greater comfort than the hopes of seeing you here soon; but your letter has cast a very great damp upon us all. I think you have been in a very extraordinary manner obliged to Dr. Douglas, and whatever opinion I may have of his present offer, or however unwilling I may be to consent to it, still I must thankfully own it, as a particular instance of his kindness to you. I surely must soon expect to be beyond this side of time, considering my age and present indisposition, being for some days past confined to my bed with sickness, and a severe fit of the gravel, and would be glad to have you near me for the little while I shall be in this world; though at the same time I should be sorry to hinder you from making your way in the world, the best way you can.—I wish you to consider well what you do.—With Dr. Cullen you may be very comfortably settled, and make money, and if you miss this opportunity now, you cannot be sure of it at another time —Dr. Douglas's kind offer is only for a time. He may die before you come home or are settled, and leave you without friends at a great enough uncertainty. I suppose now you know very well the difference between the expence of living at home and abroad, and that perhaps cloaths and pocket-money may cost you more than your whole expense at home would do. You know my willingness to assist you, but you know too, that already I have gone fully as far as my numerous family will allow of.—You must now do something for yourself. Consider all these things, and if you can persuade me that it is for your good, I will

not be against it."

The prophetic words written by the old man were shortly realized, for John Hunter, Sr., died October 30th, in the same year (1741), at the ripe old age of seventy-eight.

James, though he now became the nominal head of the family, did not remain at home for long. Sir Everard Home tells us that he "was brought up to the law, as a writer to the signet in Edinburgh, but in the year 1742 [probably late in the year 1741] went to London on a visit to his brother William, who was at that time a teacher of anatomy, and so much was he captivated by the pursuits in which he found his brother engaged, that he purposed to follow them himself, and become a practitioner in physic.* His health however was so much impaired by his application to anatomy, that he was obliged to return to Long Calderwood, where he died of a spitting of blood, in the twenty-eighth year of his age [April 11th, 1745]."

During James's sojourn in London with William, another tragedy was occurring at Long Calderwood; for the brothers received news that Isabel, their youngest sister who was only sixteen years of age, was ailing; and William wrote his mother, giving advice, encouragement and sympathy. "I am heartily concerned for my dear little sister Tibbie, but I hope the Mare's milk and the Fole together will surely recover her, for you know she likes Foles and Calfs. Tell her she must write me about the White Hamilton Stork [stirk?], and that Jamie and I will pay her a visit as soon as we have got our pockets full of gold to buy her a country seat, and give her what horses and other things she wants." Hardly had this letter reached Scotland before death came to "Tibbie," on July 30th, 1742; the third to occur in this home during the short period of a little over a year.

There were now only four left at home; Mrs. Hunter, Janet, Dorothy, and "Johnnie." Janet married a ne'er-do-well named Buchanan, some time during the year 1748. "This marriage gave the family great concern;" wrote Sir Everard Home; "for the qualities which had rendered Mr. Buchanan agreeable, led him into dissipation, and made him neglect his business."

John Hunter was thirteen years old when his father died; a sturdy, heavily built, red-haired lad less than five feet in height, with a de-

* "The late Dr. Hunter has been heard to remark, that if he [James] had lived to practice physic in London, nothing could have prevented him from rising to the top of his profession." (Home)

termined jaw, who enjoyed outdoor life and despised school. "He was sent to grammar-school," wrote Sir Everard Home, "but not having a turn for languages, nor being sufficiently under control, he neglected his studies, and spent the greatest part of his time in country amusements." He was self-willed, short-tempered and given to tantrums ending in tears, when crossed in some desire. Joanna Baillie, his niece, wrote that "he was extremely indulged, and so humoursome that he would often, when a pretty big boy, sit for hours together crying when he could not get what he wanted; and could not be taught to read but with the greatest difficulty, and long after the age when other children read English fluently." I think, today, it would be said that he was emotionally unadjusted. "Jock" was taken from school by his fond and indulgent mother soon after her husband's death in order, it is said, that he might help on the farm, as both James and William were away in London and Dorothy alone remained. This, in all probability, was to the liking of "Jock" who, it seems, had little respect for the subjects taught at school and enjoyed roaming through the countryside.

"When I was a boy" [he said in later years] "it was a little reading and writing, a great deal of spelling and figures, geography which never got beyond the dullest statistics, and a little philosophy, and chemistry as dry as sawdust, and as valuable for deadening purpose. I wanted to know about the clouds and the grasses, why leaves changed colour in the autumn. I watched the ants, bees, birds, tadpoles, and caddis worms. I pestered people with questions about what nobody knew or cared anything about."

From these remarks it becomes evident that even at this early age John Hunter possessed that insatiable curiosity and scepticism of mind which, in later life, gave him the endurance to push his inquiries until he obtained, to his own satisfaction, the correct solution of the investigation. As a helper on the farm, it is feared, he was of little assistance in the daily chores, but if there was a sick cow or mare in foal, we can be sure that the boy was in attendance and spared neither time nor inconvenience in doing what he could to help. Apparently all the members of the family were interested in animal life of both the domestic and wild creatures, but to "Jock" there seems to have been no other interest. All through his writings, in the *Philosophical Transactions*, in *Animal Oeconomy*, and in the *Essays*, edited by Sir Richard Owen, can be found abundant evidence of observations made during these

early years he spent at Long Calderwood. Like many another boy who has little or no interest in the subjects taught at school, the youthful John Hunter gave every available moment to investigating animal life and observing the habits of animals, birds, insects, and fish. Starting early in life, he developed an antipathy for the written word of authority and substituted inquiry for obtaining what he wished to know. It is hard to believe that he was a wayward boy, as some of his biographers seem to imply; but, being self-willed and determined in character, it appears he refused to learn in the accepted way at grammar school and chose his own method of acquiring knowledge through observation in the field of study that most interested his inquisitive mind. Discovering that inquiry was the really accurate method of learning the truth from nature, he soon lost respect for authors who made mere compilations from the books of older writers.

Reaching the age of twenty and having found no agreeable vocation, John Hunter decided to join his brother in London. Writing to William, he requested "that he would allow him to come to London upon a visit, making at the same time an offer to be his assistant in his anatomical researches; or if that proposal should not be accepted, expressing a wish to go into the army." His brother having accepted his offer, the young man set our during the early autumn of the year 1748 on his long journey to the Great Metropolis.

The following spring the two brothers in London were informed of their sister Janet's death, through a letter from their faithful friend:

Glasgow, 29th May, 1749

"My Dear Willie,

It is with pain I write to you, but it is to save your mother more pain in doing it herself. Your sister Mrs. Buchanan died Friday night last. It was after being valetudinary for some years; . . . Your mother and Dorothy, bating what they feel on this occasion, are otherwise well. I hope you will be very careful of your own health, that you may long be—what you will be while you live—a great comfort to them and to all your friends. I am, from the bottom of my heart, dear Willie, Yours

WILLIAM CULLEN.

William Hunter visited Long Calderwood for the last time during the autumn of 1750. The only occupants of the homestead were now his mother, whose health was rapidly failing, and his one remaining

sister, Dorothy. We can be sure that at this time "Willie" renewed his old friendship with William Cullen, which after this was to be continued on to the year of his death only by means of an exchange of intimate letters and mutual acts of kindness; for these busy men were never to meet again. To his gratification, on October 24th the University of Glasgow saw fit to confer upon him the degree of Doctor of Medicine and, in the following March, his name was entered upon the "Roll" of the Faculty of Physicians and Surgeons of Glasgow.

"During this visit he shewed his attachment to his little paternal inheritance," wrote Simmons, "by giving many instructions for repairing and improving it, and for purchasing any adjoining lands that might be offered for sale. As he and Dr. Cullen were riding one day in a low part of the country, the latter, pointing out to him Long Calderwood at a considerable distance, remarked how conspicuous it appeared. 'Well'—said he, with some degree of energy—'if I live I shall make it still more conspicuous.' "

William Hunter surely must have found it difficult to leave his childhood home where his mother lay so ill, but pressing activities called for his presence in London where Mr. John Symonds, his assistant, with the help of John, whose anatomical knowledge was beginning to rival that of his brother, were conducting the classes during his absence. Though he must have realized that he was never to see his mother again, he undoubtedly obtained some comfort from the knowledge that she would be tenderly nursed by his sister, under the wise direction of his devoted friend. Six months later we find Cullen reporting to him on her condition. "Her ailments continue very obstinate . . .," he wrote, "I have endeavored to engage her in some exercise. She has tried going on horseback, and going in a cart and in a car, but every kind of motion raises her pain so much, that we cannot persuade her to repeat the trials. Upon the whole, I am persuaded some scirrhosity is forming in the stomach, which gives me a very disagreeable prospect with regard to her. She says nothing now about Johnie's coming down; but I know, in her present temper, it would have pleased her much if he had." Poor woman, she pined for the sight of her last-born, her "Jockie," before she died. However, this was not to be, for the practical William, writing from London, brusquely informed Cullen of his decision on this matter. "But I cannot consent this season to her request," he wrote, "for my brother's sake, for my own sake, and even for my mother's sake. It

would be every way a bad scheme. I have wrote of it to her, and I hope she will consider better of it, and find that it is really a whim begot of sickness and low spirits." Mrs. Hunter died November 3rd, 1751, at the age of sixty-six. Cullen, writing four weeks before this event, tells of her progressive weakness and advises William to delay no longer in writing to her or to Dorothy. "It gives some relief to Dorothy," he wrote, "that now your mother seems to be declining fast, it is with very little of those pains which formerly afflicted her." After assuring William that he would be present during his "mother's last moments" and arrange the funeral, he wrote—"my chief care shall be bestowed on Dorothy. As you have no objection to my plan with regard to her, I shall do as I proposed, that is, as soon as your mother is interred, take Dorothy to my house, where I am sure she will find a very hearty welcome." William Hunter, in replying after his mother's death, expresses his satisfaction for the "kind attendance" of his friend during his mother's long illness and then discusses a plan for his sister's future. "Our next care must be about my sister;" he wrote, "who has recommended herself strongly to me by her indefatigable tenderness. Poor girl, I pity her from my soul. Your offer with regard to her is generous and friendly. I leave her to be determined by you and her friends. In the mean time, I would propose that she should stay in Scotland till the spring, both for the sake of good weather, and that my great hurry may be over, and that we may have some time to consider how our little affairs are to be managed in Scotland after she leaves the place. Then I should propose that she come up to me, or perhaps I may then send my brother to bring her." As far as we know, this plan was carried through, for John Hunter left for Scotland in the spring of 1752, as soon as the winter session at his brother's anatomical school was finished, and returned during the early autumn accompanied by his sister Dorothy, who was to reside with her brothers in the Great Piazza, Covent Garden.

We hear nothing further of anyone residing at Long Calderwood until the year 1778, when Dorothy, then a widow, returned to the old homestead with her two daughters. She had married the Reverend James Baillie, a minister at Shots, in 1758. Her daughter Agnes was born a year later and, on October 24th, 1760, a son was born, who was named Matthew. Soon after, moving to Bothwell, a town upon the Clyde near Hamilton, her second daughter was born on September 11th, 1762 and was named Joanna, for her uncle John Hunter. The family then moved

to Hamilton in the year 1769 and, when Dr. Baillie was appointed Professor of Divinity at the University in 1776, they moved to Glasgow. But his tenure of office in the "College" was short, for death claimed him two years later. Mrs. Baillie, with her daughters, then moved to Long Calderwood, her son having entered Balliol College, Oxford. During his vacations, Matthew studied anatomy at the Great Windmill Street School in London, where he won the respect and deep affection of his uncle, William Hunter, who taught him the art of observation and "communicated to him his love of science." His mother, at the time of her son's departure for the University, wrote her brother: "I have furnished him out in the best manner my situation could afford. I now give him over to you. Be a father to him—you the only father he has alive. I hope you shall never be ashamed of his conduct, but that he shall obey your directions in everything."

In the meantime Joanna, who had received her schooling in Glasgow, was beginning to develop great talents. She is said to have shown ability in music and drawing but, in addition, an exceptional aptitude for dramatics and composition. At Long Calderwood Joanna was thrown on her own resources; besides the outdoor life, where she came to know the country folk residing on neighboring farms, "her chief enjoyment was found in books."

After William Hunter died on March 30, 1783, Mrs. Baillie and her daughters moved to London to reside with her son, who had inherited his uncle's entire estate. Here Dorothy Hunter Baillie lived until her death, at a good old age, in the year 1807; to see her son become a great pathologist and the most outstanding physician of London, and her daughter Joanna rise to fame as a dramatist and poet, whom her friend Sir Walter Scott named "The Immortal Joanna."

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

APRIL 1—*The New York Academy of Medicine.* Executive session—a] Reading of the minutes; b] Presentation of Certificates of Fellowship. ¶ The Eighteenth Hermann M. Biggs Memorial Lecture, under the auspices of the Committee on Public Health Relations; Malaria and Its Influence on World Health by Lieutenant Colonel Paul F. Russell, Medical Department, Army of the United States, Chief, Tropical Disease and Malaria Control Section, Division of Preventive Medicine, Office of the Surgeon General. ¶ Report on election of Fellows.

APRIL 15—*The Harvey Society in affiliation with The New York Academy of Medicine.* The Seventh Harvey Lecture, "Sterilization of Air with Glycol Vapors," O. H. Robertson, Professor of Medicine, University of Chicago School of Medicine.

MAY 20—*The Harvey Society in affiliation with The New York Academy of Medicine.* The Eighth Harvey Lecture, "Nutrition Under Wartime Conditions." V. P. Sydenstricker, Professor of Medicine, University of Georgia School of Medicine. ¶ Report on election of Academy Fellows.

APRIL 2—*Surgery. Program from the Surgical Services of the Goldwater Memorial Hospital.* ¶ Executive session—a] Reading of the Minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Introductory remarks—Condict W. Cutler, Jr. ¶ Case presentations—a] Extensive tuberculosis of the chest wall, operative result, Louis Carp; b] Disabling chronic arthritis complicated by acute gangrenous cholecystitis, cholecystectomy followed by cure of arthritis, Charles W. Lester; c] Block resection of sigmoid and adherent structures for carcinoma, with perforation and secondary abscess of abdominal wall, George H. Humphreys (by invitation); d] Hyperthyroidism complicated by chronic cardiac disease, post-operative results, Grant P. Pennoyer; e] Cases illustrating a method of handling painful extremities in peripheral vascular diseases, Margaret Stanley-Brown; f] Gangrene of the lower extremity, supracondylar amputation under crymal anesthesia, Wilson E. Alsop; g] Arthritic hip joints, arthroplasty with the use of vitallium cups, William A. Walker (by invitation). ¶ General discussion by W. Howard Barber.

APRIL 6—*Dermatology and Syphilology.* ¶ Presentation of cases—a] From Beth Israel Hospital; b] From the Good Samaritan Dispensary; c] Miscellaneous cases. ¶ Discussion. ¶ Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee.

APRIL 8—*Pediatrics.* ¶ Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] Delays in development of language in children, Samuel T. Orton; b] Emotional disturbances affecting speech, Frederick H. Allen (by invitation), Director, Philadelphia Child Guidance Clinic.

APRIL 13—*Combined Meeting. Neurology and Psychiatry and the New York Neurological Society.* ¶ Papers of the evening—*Psychosomatic disorders*—a] The historical and scientific issues in psychosomatic problems, Gregory Zilboorg; b] Physiological principles underlying psychosomatic disorders, Donal Sheehan (by invitation); c] The basis of classification of disorders from the psychosomatic standpoint, Lawrence S. Kubie; d] Psychosomatic diagnosis with special reference to cardiovascular syndromes, H. Flanders Dunbar. ¶ Discussion—

Frank Freemont-Smith, Emanuel D. Friedman, Louis Leiter (by invitation), Bettina Warburg, Edward Weiss (by invitation), Philadelphia, Harold G. Wolff. ¶ Executive session, nomination of Officers and one member of the Advisory Committee of the Section.

APRIL 19—*Ophthalmology.* ¶ Instruction hour—7:30 to 8:15 oclock—Moving pictures. ¶ Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] Peripheral retinal holes without detachment, Arnold Knapp; b] A case of chronic mercurialism exhibiting a colored reflex from the anterior lens capsule, Walter S. Atkinson. Discussion by Maynard C. Wheeler; c] Pathology following injuries of the eyes, Georgiana Theobald (by invitation); d] Unusual manifestations of malignant melanoma of the uveal tract, Algernon B. Reese. Discussion by Bernard Samuels; e] A combined intracranial and orbital operation for retinoblastoma, Bronson S. Ray, John M. McLean. Discussion by E. B. Burchell (by invitation), Bernard Samuels; f] Case report: Subconjunctival dislocation of the lens with sympathetic ophthalmia, Charles Perera.

APRIL 20—*Medicine.* ¶ Reading of the minutes. ¶ Paper of the evening—The role of the internist in the management of sterility, William H. Cary (by invitation). ¶ General discussion. ¶ Executive session—Nomination of Section Officers and one member of the Advisory Committee.

APRIL 21—*Genito-Urinary Surgery.* ¶ Reading of the minutes. ¶ Case reports—Medullary tumor of the adrenal—pheochromocytoma, Joseph Tenenbaum. Case reports of interesting renal malignancies invited. ¶ Paper of the evening—Classification of renal tumors, Meyer M. Melicow (by invitation). ¶ General discussion. ¶ Executive session—Nomination of Section Officers and one member of Advisory Committee.

APRIL 21—*Otolaryngology.* ¶ Executive session—Reading of the minutes. ¶ Case presentations—a] Shrapnel in sphenoid sinus causing blindness, removal with recovery, Irving B. Goldman, Knut Houck (by invitation); b] Recurrent oncocytoma of the trachea, Arthur Palmer, Nathan Chandler Foot. ¶ General discussion.

APRIL 16—*Orthopedic Surgery.* ¶ Reading of the minutes. ¶ Papers of the evening—a] Roentgen soft tissue studies in an orthopedic hospital, Raymond Lewis. Discussion by Stephen White; b] Ocular torticollis—differential diagnosis, Loren Guy. Discussion by Leon Lantzounis. ¶ General discussion. ¶ Executive session—Nomination of Section Officers and one member of Advisory Committee.

APRIL 27—*Obstetrics and Gynecology.* ¶ Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Case report—Polyneuritis of pregnancy, with review of the literature and a case report, Julius Lebovitz (by invitation). ¶ Papers of the evening—a] Clinical evaluation of hysterography Morris A. Goldberger; b] A proposed annual textbook of gynecology. Each subject individually and compactly compiled in brief, concise and complete form. Facts on medications, etc. condensed for quick review. Pages and chapters illustrated by lantern slides, Robert J. Lowrie. ¶ General discussion.

MAY 3—*Dermatology and Syphilology.* ¶ Presentation of cases—a] From the New York Hospital and Cornell Medical College; b] From the Brooklyn Jewish Hospital; c] Miscellaneous Cases. ¶ Discussion. ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—For Chairman: David Bloom, For Secretary: George Morris Lewis, For Member of Advisory Committee: Elias William Abramowitz.

MAY 7—*Surgery.* ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—For Chairman: Louis Carp, For Secretary: Clay Ray Murray, For Member of Advisory Committee: John V. Bohrer. ¶ Case presentations—a] Cholecystectomy. Subsequent choledochotomy and choledochoduodenostomy, two-year follow-up, Harold Brown Keyes; b] Choledochoduodenostomy for recurring common duct infection and formation of stones, Thomas H. Russell; c] Endocholedochal sphincterotomy for dyskinesia, Ralph Colp; d] Primary carcinoma of the common bile duct, Radial resection, five-year follow-up, John H. Garlock. ¶ Papers of the evening—a] Acute cholecytitis, present trends in treatment and why opinions differ, Henry F. Graham (by invitation); b] A five-year experience in biliary tract surgery, Pro. V. Prewitt. ¶ General discussion—Grant P. Pennoyer, Philip D. Allen.

MAY 12—*Combined Meeting. Neurology and Psychiatry and Historical and Cultural Medicine.* ¶ Executive session—a] Officers and member of Advisory Committee elected for 1943-44; Section of Neurology and Psychiatry—Chairman: Gerald R. Jameison, Secretary: Harold G. Wolff, Member of Advisory Committee: Charles Davison; b] Election of Officers and members of Advisory Committee; Section of Historical and Cultural Medicine—For Chairman: Edward F. Hartung, For Secretary: Paul E. Bechet; For Member of Advisory Committee: Herman Goodman. ¶ Paper of the evening—Descartes and modern psychiatric thought, Iago Galdston, A. A. Brill. Discussion by Nolan D. C. Lewis and Tracy J. Putnam.

MAY 13—*Pediatrics.* ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—For Chairman: Edith M. Lincoln, For Secretary: John D. Lyttle, For Member of Advisory Committee: Charles Hendee Smith. ¶ Presentation of single case reports—a] St. Luke's Hospital—Congenital multiple atresias of the intestine, Peter Duncan (by invitation); b] Mt. Sinai Hospital—A case of hypoglobulinemia, Jerome Greenbaum (by invitation). Discussion opened by Bela Schick; c] Beth Israel Hospital—Prolonged tetany of the newborn, Jacques M. Lewis; d] Willard Parker Hospital—Heart block in diphtheria with recovery, William Kershaw (by invitation). Discussion opened by Cary Eggleston, Edward A. Burkhardt (by invitation); e] New York Hospital—A diagnostic problem in a premature infant, Thomas F. Henley (by invitation); f] Babies Hospital—Fever of unknown origin; an unusual solution, Rustin McIntosh; g] New York Post-Graduate Hospital—A case of non-suppurative paniculitis, Vincent DeP. Larkin (by invitation).

MAY 17—*Ophthalmology.* ¶ Instruction hour 7:00 to 7:45 o'clock—Technique of the preparation of eye specimens from enucleation to microscope, E. B. Burchell (by invitation). ¶ Papers of the evening, 8:00 o'clock—a] A case of spasm of the retinal arteries, C. Ray Franklin (by invitation); b] Recurrence of tobacco-alcohol amblyopia, Frank D. Carroll. ¶ Executive session, 8:30 o'clock—a] Reading of the minutes; b] Election of Section Officers and one member of Advisory Committee—For Chairman: Frank C. Keil, For Secretary—Willis S. Knighton; For Member of Advisory Committee: Daniel B. Kirby. ¶ Papers of the evening (*continued*)—c] The prophylactic use of sulfadiazine in cataract extraction, Jack Guyton (by invitation); d] A case of hemangioma of the choroid, Ralph I. Lloyd; e] A case of seminoma metastatic, Fritz Bloch (by invitation); f] Embryology of the eye—a new method of demonstration, George H. Paff (by invitation); g] Congenital cyst of the optic nerve, Sigmund A. Agatston; h] An original limbal suture for corneal transplants, Vito LaRocca (by invitation).

MAY 18—*Medicine.* ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—For Chairman: Horace Baldwin, For Secretary: William S. Tillett; For Member of Advisory Committee: G. Jarvis Coffin. ¶ Papers of the evening—a] Congenital phlebectasia of lower extremity, M. Kert (by invitation), The Mount Sinai Hospital. Discussion by A. Grishman (by invitation); b] Factors influencing the citric acid metabolism in man, Thomas P. Almy (by invitation), Department of Medicine, New York Hospital. Discussion by Ephriam Shorr (by invitation); c] Chylothorax and chylous ascites, James McCormack (by invitation), Bellevue Hospital. Discussion by William S. Tillett.

MAY 19—*Genito-Urinary Surgery.* ¶ Reading of the minutes. ¶ Papers of the evening—a] The use of radium in chronic anterior urethral strictures, H. Haig Kasabach (by invitation), b] Laminography as an aid in the visualization of the suprarenal gland, Seymour F. Wilhelm; c] Interesting urologic conditions encountered in the Military Service, Major Thomas P. Sheerer (by invitation). ¶ General discussion. ¶ Executive session—Election of officers; Report of Nominating Committee—For Chairman: John H. Rathbone, For Secretary: E. King Morgan, For Member of Advisory Committee: Major Frank Hamm.

MAY 19—*Otolaryngology.* ¶ Reading of the minutes. ¶ Papers of the evening—a] Radiation therapy in otolaryngology (Case presentations: lantern slides), Ira I. Kaplan; b] Variations in the anatomy of the temporal bone (specimens: lantern slide demonstrations), E. B. Burchell (by invitation). ¶ General discussion. ¶ Executive session—Election of Section Officers and member of Advisory Committee—For Chairman: Victor C. McCuaig, For Secretary: Jackson A. Seward, For Member of Advisory Committee: John Winston Fowlkes.

MAY 21—*Orthopedic Surgery.* ¶ Executive Session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—For Chairman: Halford Hallock, For Secretary: John R. Cobb, For Member of Advisory Committee—John C. McCauley, Jr. ¶ Presentation of case reports—a] Resection of the elbow for complete ankylosis, Samuel W. Boorstein; b] A case of generalized carcinomatosis in a child, Henry Briggin; c] Translocation of the fibula with its attached structures for pseudoarthrosis of the tibia; fracture of the transplant followed by healing, Joseph Buchman; d] Improvement of carcinomatous metastasis following orchidectomy, John A. Taylor; e] Complications following removal of ruptured nuclei pulposus, Leon Lantzounis; f] Adult club foot, operative correction, Edward M. Winant (by invitation); g] Paget's disease with sarcomatous degeneration, John M. Pendy (by invitation). ¶ General discussion.

MAY 25—*Obstetrics and Gynecology.* ¶ Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee—For Chairman: Robert J. Lowrie, For Secretary: James P. Marr, For Member of Advisory Committee: William T. Kennedy. ¶ Case reports—a] Antepartum diagnosis of defective cesarean scar, confirmed by operation: a report of two cases, A. J. Rongy; b] Two cases illustrating the effect of the pressure of uterine fibroids on the ureter, S. Wimpfheimer. ¶ Paper of the evening—a] Study of human uterine contractions with the aid of a photoelectric water manometer, I. C. Rubin, S. Feitelberg (by invitation), A. M. Davis (by invitation). ¶ General discussion.

AFFILIATED SOCIETIES

APRIL 19—*New York Roentgen Society in affiliation with The New York Academy of Medicine.* ¶ Papers of the evening—a] Fibrous dysplasia affecting one, sev-

eral or many bones, Louis Lichtenstein (by invitation); b] Giant cell tumor of bone; its differentiation from lesions confused with it, Henry L. Jaffe (by invitation); c] Radiographic aids in orthopedic surgery, Samuel Jahss (by invitation); d] Posttraumatic osteoporosis (osteochondritis), Joseph Buchman (by invitation). ¶ General discussion.

APRIL 22—*New York Pathological Society in affiliation with The New York Academy of Medicine.* ¶ Papers of the evening—a] Observations on the pathology of osteopetrosis (marble bone disease), Bernard Pines (by invitation); b] The determining influence of the dietary ratio of calcium and phosphorus upon the size of the parathyroid, Herbert C. Stoerk (by invitation), William H. Carnes (by invitation); c] Postmortem findings after dicoumarin therapy, Max Lederer, Edmund Shlevin (by invitation); d] Anti-Rh sera and other aspects of iso-immunization by pregnancy, Philip Levine (by invitation). ¶ Executive session.

MAY 17—*New York Roentgen Society in affiliation with The New York Academy of Medicine.* ¶ Papers of the evening—a] A simplified method of calculating radium dosage, Bernard Wolff (by invitation); b] Depth-dose measurements in roentgen therapy of 100 to 135 K. V., Carl Braestrup; c] Roentgen therapy in cases of osteomyelitis of the pubis, J. R. Freid; d] Roentgen therapy in cases of pelvic tuberculosis, Harriet C. McIntosh; e] Roentgen therapy in cases of Marie Strumpell spondylitis, Haig H. Kasabach. ¶ General discussion. ¶ Executive session.

MAY 27—*New York Pathological Society in affiliation with The New York Academy of Medicine.* ¶ Case presentations—a] Fatal myocarditis in a case of trichinosis, Donald Parker (by invitation), b] Case of telangiostenosis manifesting the clinical picture of periarteritis nodosa, John B. Miale (by invitation), Jacob Furth. ¶ Papers of the evening—a] Pathologic effects of certain common war gases, Capt. Arthur M. Ginzler, M. C.; b] Bronchial adenoma: Distinctive features of its pathology, clinical manifestations, and therapy, Coleman B. Rabin, Harold Neuhof (by invitation). ¶ Executive session.

CLINICAL RESEARCH MEETING

MAY 27—*Arranged by the Committee on Medical Education—Medical Division,* (Room 20), B. S. Oppenheimer, Presiding Officer—1. The production of a sulfonamide antagonist and a sulfonamide potentiator by the tubercle bacillus, Walsh McDermott, Alice Tracy; 2. Further studies on penicillin as a chemotherapeutic agent, Martin H. Dawson, G. L. Hobby, K. Meyer, E. Chaffee; 3. Certain new considerations in local sulfonamide therapy, Charles L. Fox, Jr.; 4. Studies on the etiology of the renal shutdown following crush injuries, R. J. Bing; 5. The complement-fixation test for lymphogranuloma venereum: Results obtained with its use, Arthur W. Grace; 6. Acute infectious lymphocytosis, Carl H. Smith; 7. Probable mechanism by which somatic changes in certain emotional states are mediated, A. T. Milhorat, S. M. Small, E. J. Doty, W. E. Bartels; 8. Physiopathological aspect of muscles in infantile paralysis, J. Moldaver; 9. Neurohormonal regulation of water balance: Studies in patients with diabetes insipidus, Thomas Hodge McGavack; 10. Titration and neutralization of the Western strain of equine encephalomyelitis virus in tissue culture, C. H. Huang; 11. Nitrogen retention, creatinuria, and other effects of the treatment of Simmonds disease, with methyl testosterone, Sidney C. Werner, Randolph West; 12. The relationship between blood concentration and blood volume in cardiac decompensation, Joseph DiPalma, Philip E. Kendall.
Surgical Division, Raymond P. Sullivan, Presiding Officer—1. Study of the cir-

culation in clinical shock, A. Cournand, R. L. Riley, E. S. Breed, D. W. Richards, Jr.; 2. Traumatic shock, Magnus I. Gregersen; 3. Renal circulation in shock, Henry Lauson (Bellevue group); 4. The effect of sodium thiosulphate on the blood, Linn J. Boyd, Louis Greenwald, Joseph Litwins; 5. Modification in surgical treatment of herniated nucleus pulposus, Leo M. Davidoff; 6. Plasma-clot suture of peripheral nerves, I. M. Tarlov; 7. A new practical method for the subcutaneous administration of heparin, Leo Loewe, Philip Rosenblatt; 8. The role of the lymphatics in ascending urinary infections, John L. Alley; 9. Test of viability of the gut in local obstructions, John Herrlin, Jr., S. Thomas Glasser.

Obstetrics and Gynecology, Albert H. Aldridge, Presiding Officer—1. A rapid pregnancy test (two to six hours), U. J. Salmon, S. H. Geist, C. S. Poole, A. A. Salmon, B.S.; 2. Nutritional deficiency in the etiology of menorrhagia, metrorrhagia, cystic mastitis and premenstrual tension: Treatment with vitamin B complex, Morton S. Biskind, Gerson R. Biskind, Leonard H. Biskind; 3. The concentration of vitamin A in the blood plasma during pregnancy, J. M. Lewis, O. Bodansky, M. C. Lilienfeld; 4. Measurement and recording of intrauterine pressure, Sergei Feitelberg, I. C. Rubin; 5. Vitamin D in human milk, Louis J. Polskin, Benjamin Kramer, Albert E. Sobel; 6. A new experimental laboratory animal, the South African clawed frog (Xenopus laevis): Its use in pregnancy diagnosis, hormone assays and endocrine evaluations, Abner I. Weisman, Christopher W. Coates.

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